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Original Research Article

Relative adrenal insufficiency in non-critically ill liver cirrhosis

Dipen Agrawal, G. R. Srinivas Rao, D. Viswanath Reddy*, B. Ravi Shankar

Department of Medical Gastroenterology, Yashoda Hospitals, Secunderabad, Telangana, India

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***Correspondence:**
Dr. D. Viswanath Reddy,
E-mail: viswanathdr@yahoo.com

ABSTRACT

Background: Endocrinopathy like adrenal insufficiency (AI) is being increasingly recognised in patients with liver cirrhosis. It is characterized by a relative decrease in serum cortisol level with respect to increasing stress as occurs in sepsis & has been associated with increased morbidity and mortality. This study aimed to find the prevalence of Adrenal insufficiency and low HDL in non-critically ill chronic liver disease (CLD) patients i.e. patients without sepsis, bleed or dehydration.
Methodology: A cross-sectional study including 100 non-critically ill CLD patients aged 20 -80 years. Model for end stage liver disease (MELD) scores and the Child Turcotte Pugh scores (CTP) were used to assess the severity of liver disease. Basal cortisol level was measured & after one hour of short synacthen test (SST), peak and delta cortisol levels were measured in order to assess adrenal function. Biochemical parameters including HDL levels were also assayed.
Results: This study included 76 male and 24 female CLD patients. Prevalence of AI was highest in females of age 41-60 years. Alcohol (61%) was the most common etiology, followed by MASLD and HBV. Prevalence of AI was 55.6%, 60.5% and 65.9% in CTP class A, B and C respectively. Prevalence of AI in the high MELD (>15) group was 66.7% and 50% in the low MELD (<14) group. Low HDL and AI were reported in CTP classes B and C.
Conclusion: Adrenal insufficiency is common in patients with non-critically ill chronic liver disease; which increases with severity of disease; and whose HDL levels are low.

Keywords: Adrenal insufficiency, CLD, CTP, MELD, HDL, Etiology

INTRODUCTION

Hepato-adrenal syndrome, also known as adrenal insufficiency in liver cirrhosis, is currently one of the most prevalent conditions associated with hypotension & hyponatremia and has a significant impact on the prognosis of these patients.[1,2]

Septic shock and liver failure share many similarities which is characterized by the presence of hyperdynamic circulation, characterized by elevated cardiac output, reduced systemic vascular resistance, and a low mean arterial pressure.[3] Studies on patients with liver disease reveal that the prevalence of Adrenal insufficiency varies widely, which may be related to the heterogeneity of the cases under study as well as the use of different diagnostic methods and definitional criteria.[4] Adrenal insufficiency also exists in stable patients with cirrhosis.[5] However, no sufficient data exists regarding the prevalence or differences in the various causes of cirrhosis with Adrenal insufficiency. Studies show that Adrenal insufficiency is frequent in patients with stable cirrhosis and is related to the liver disease severity.[6]

Moreover, various studies are available regarding the clinical significance of Adrenal insufficiency in liver failure or cirrhotic patients with septic shock, whereas only few studies have been reported regarding the prevalence in stable cirrhosis.[7] Since the liver plays a vital role in homeostasis of cholesterol, hypocholesterolaemia often occurs in patients with chronic liver disease.[8] There is high prevalence of decrease in serum lipids and lipoproteins in

cirrhotic patients, which increases gradually with the severity of disease.[9] HDL is the substrate for adrenal steroidogenesis & previous studies show that HDL-C is an independent predictor of mortality in patients with cirrhosis and associated with the severity of sepsis.[10] However, studies with regard to the effects of liver disease on lipid profiles have reached contradictory findings in different etiologies.[11]

This study aims to estimate the prevalence of AI and low HDL in non-critically ill liver cirrhotic patients and assess any possible correlation with the etiology, severity of liver disease and clinical characteristics of the patients.

METHODS

This is a cross-sectional observational study & included 100 consecutive non critically ill chronic liver disease (CLD) individuals from Gastroenterology department of Yashoda Hospitals, Secunderabad from January 2019 to June 2020. Approval from the Institutional Ethics Committee was obtained. Written informed consent was obtained from enrolled subjects.

The study included male and female patients, aged 20 to 80 years who are hemodynamically stable with a confirmed diagnosis of non-critically ill chronic liver disease i.e., with no GI bleed, hepatic encephalopathy, hepatorenal syndrome. The study excluded patients with liver transplantation, active tuberculosis, Cushing's syndrome, malignancy, hemodynamically unstable, prolonged steroid use, pregnant women and patients using immunosuppressive therapy.

After appropriate consent, all patients underwent detailed clinical examination and an overnight fast, an automated biochemical analysis, which included liver function test, prothrombin time, renal function test, serum electrolyte serum lipid profile and fasting total cortisol levels. Following base line investigations, patients received an intramuscular injection of 25 units of acton prolongatum (synthetic ACTH manufactured by Ferring Pharmaceuticals). After one hour of injection, serum total cortisol and delta cortisol levels were assessed by enhanced chemiluminescence method (post-stimulation cortisol level). The MELD scores and the CTP scores were used to assess the severity of liver disease. Adrenal insufficiency was diagnosed based on any low level of serum cortisol i.e. Serum basal cortisol ≤5 µg/dl or Serum delta cortisol ≤9 µg/dl or Serum peak cortisol ≤18 µg/dl. IBM SPSS V21 was used to perform statistical analysis. Mean±SD was used to present the results of continuous measurements, while number (%) was used to present the results of categorical measurements. The significant associations of study parameters on a categorical scale between two or more groups were determined using the chi-square test. A p value of less than 0.05 was deemed statistically significant. Coefficient of variance was used for comparison of diagnostic methods of adrenal insufficiency.

RESULTS

One hundred consecutive patients of non-critically ill CLD were included in the study. 71% of the patients were between the ages of 41 and 60, 20% between the ages of 61 and 80, and 9% between 20 and 40 years.

Prevalence of AI was 66.2% in the age group of 41-60, 55.6% in 20–40-year-old patients, and 50% in range of 61-80 years with no age-related significant association (p>0.05). Males (76%) outnumbered the females (24%) in this study. Prevalence of AI was higher in females than males. Nevertheless, there was no significant statistical difference in adrenal function between males and females (p=0.45).

Adrenal insufficiency was observed in 62 out of 100 subjects. Most of the patients considered for this study were in CTP class B and CTP class C and the prevalence of Adrenal insufficiency was also high in these groups. Prevalence of AI in CTP class A is 55.6%, Class B is 60.5% and Class C is 65.9%. Results also showed that 72% had a high MELD score (>14) and 28% had low MELD (≤14) score. Although the prevalence of adrenal insufficiency was 50% in the low MELD group and 66.7% in the high MELD group, the differences are statistically insignificant (p=0.99). In the present study, alcohol was the leading cause of chronic liver disease in 61% of patients, followed by MASLD (23%), HBV (11%) and the rest were HCV (3%), PBC (1%), Cardiac cirrhosis (1%) (Table 1).

Serum albumin levels were significantly lower (p=0.008) in patients with Adrenal insufficiency compared to patients without Adrenal insufficiency and INR was significantly higher in patients with AI (p=0.045). Additionally, in patients with AI, total bilirubin was higher with no statistical significance (p=0.453) compared to patients without AI. Haemoglobin, HDL, LDL, total cholesterol, sodium and creatinine values were lower in patients with Adrenal insufficiency which were again statistically insignificant (p=0.312, p=0.682, p=0.524, p=0.325, p=0.528, p=0.254 respectively) when compared to patients without adrenal insufficiency (Table 2).

AI was found in 18% by basal cortisol, 44% by delta cortisol, and 52% by peak cortisol using the SST. While comparing cortisol levels by SST, it was found that the coefficient of variation of basal & delta cortisol levels was low, indicating consistent response. It is also observed that mean values were high in peak cortisol levels (Table 3). In this study, 56 out of 89 patients (62.9%) with low HDL and 6 out of 11 patients (54.5%) with normal HDL had AI and is statistically insignificant (p=0.82) (Table 4). Prevalence of low HDL is reported 55.6% in CTP class A, 92.1% in CTP Class B, and 100% in CTP Class C which is statistically significant (p=0.000). In low MELD scores (≤14), the prevalence of low HDL is 71.4% whereas in high MELD scores (>15), it is 95.8% which is statistically significant (p=0.000) (Table 5).

Table 1: Prevalence of Adrenal insufficiency with respect to demographics, etiology, CTP & MELD scores.

Parameters		Total (n=100)	Adrenal insufficiency (n=62)	Without adrenal insufficiency (n=38)	Prevalence of adrenal insufficiency (AI) by			
					Fasting cortisol ≤5 µg/dl	Delta cortisol ≤9 µg/dl	Peak cortisol ≤18 µg/dl	Any cortisol level
Age (in years)	20-40	9	5	4	0	2	3	5
	41-60	71	47	24	15	33	43	47
	61-80	20	10	10	3	9	6	10
Gender	Female	24	13	11	13	37	39	49
	Male	76	49	27	5	7	13	13
CTP	A	18	10	8	4	8	9	10
	B	38	23	15	6	15	20	23
	C	44	29	15	8	21	23	29
MELD	≤14	28	14	14	3	11	13	14
	>14	72	48	24	15	33	39	48
Etiology	Alcohol	61	36	25	12	28	29	36
	Cardiac cirrhosis	1	1	1	0	0	1	1
	HBV	11	7	4	0	6	4	7
	NASH	23	14	9	5	10	14	14
	PBC	1	1	0	0	0	1	1
	HCV	3	3	0	1	0	3	3

Table 2: Laboratory investigations indicating the prevalence of adrenal insufficiency.

Parameter	Total sample (n=100)	Adrenal insufficiency (n=62)	Without adrenal insufficiency (n=38)	P value
Hb (g/dl)	11.1±1.2	10.9±1.4	11.4±1.4	0.312
Albumin (g/dl)	3.1±0.4	2.9±0.6	3.2±0.5	0.008
INR	1.3±0.2	1.6±0.4	1.4±0.2	0.045
HDL (mg/dl)	33.2±10.4	31.2±10.2	33.4±10.5	0.682
LDL (mg/dl)	73.5±38.6	66.6±44.2	76.8±35.4	0.524
T. bilirubin (mg/dl)	2.8±2.9	3.6±3.4	2.6±3.1	0.453
T. cholesterol (mg/dl)	118.4±48	109.5±52	122.8±46	0.325
Sodium (mEq/l)	138±5.8	134±6.5	137±4.6	0.528
Creatinine (mg/dl)	0.9±0.3	0.7±0.2	0.9±0.4	0.254

Table 3: Prevalence of adrenal insufficiency based on basal, delta and peak cortisol levels.

Parameter	Basal cortisol (n=100)	Delta cortisol (n=100)	Peak cortisol (n=100)
Adrenal insufficiency	18 (18%)	44 (44%)	52 (52%)
Without adrenal insufficiency	82 (82%)	56 (56%)	48 (48%)
Mean±SD (µg/dl)	11.48±9.95	11.48 ± 9.95	22.80±13.37
Variance	99.105	99.105	99.105
CV	86.68	86.68	86.68

Table 4: Prevalence of adrenal insufficiency with respect to HDL based on cortisol levels.

HDL	Prevalence of adrenal insufficiency			
	by fasting cortisol (≤5 µg/dl) (n=18)	by delta cortisol (≤9 µg/dl) (n=44)	by peak cortisol (≤18 µg/dl) (n=52)	by any cortisol level (n=62)
≤ 40 mg/dl	16	38	47	56
> 40 mg/dl	02	06	05	06

Table 5: Prevalence of HDL with respect to demographics, etiology, CTP & MELD scores.

Parameter		HDL	
		≤40 mg/dl (n=89)	>40 mg/dl (n=11)
Age group (in years)	20-40 (n=09)	08 (88.9%)	01 (11.1%)
	41-60 (n=71)	63 (88.7%	08 (11.3%)
	61-80 (n=20)	18 (90%)	02 (10%)
Gender	Female (n=24)	20 (83.3%)	04 (16.7%)
	Male (n=76)	69 (90.8)	07 (9.2%)
CTP	A (n=18)	10 (55.6%)	08 (44.4%)
	B (n=38)	35 (92.1%)	03 (7.9%)
	C (n=44)	44 (100.0%)	0 (0%)
MELD	≤14 (n=28)	20 (71.4%)	08 (28.6%)
	>14 (n=72)	69 (95.8%)	03 (4.2%)
Etiology	Alcohol (n=61)	56 (91.8%)	05 (8.2%)
	Cardiac cirrhosis (n=01)	01 (100%)	0 (0%)
	HBV (n=11)	09 (81.8%)	02 (18.2%)
	NASH (n=23)	19 (82.6%	04 (17.4%
	PBC (n=01)	01 (100%)	0 (0%)
	HCV (n=03)	3 (100%)	0 (0%)

DISCUSSION

AI is a fatal condition in which insufficient glucocorticoids are produced by the adrenal cortex leading to failure of cellular functions & stress response and is associated with increased mortality. As it is a lethal condition, early diagnosis and immediate treatment is required.[12] Although the reason for AI is not definite, some hypotheses have been suggested. These include low HDL and total cholesterol levels, increased pro-inflammatory cytokines.[13] Both stable cirrhosis and cirrhosis with critical illness (sepsis, septic shock, variceal hemorrhage) can exhibit adrenal insufficiency. All cases in the current study were stable cirrhotic patients. Adrenal insufficiency was investigated in stable or, in other words, non-critically ill cirrhotic patients and the incidence was found to be 62%.

Older adults have a higher rate of adrenal insufficiency than younger patients. The relative importance of other health problems, particularly infections, in association with adrenal insufficiency vary with age of the patient.[14] The current study findings relating age and adrenal insufficiency are in line with earlier publications. The study has shown that adrenal insufficiency increased with advancing age of the patients. In the present study, prevalence of AI was higher in women than men.

The autoimmune form of adrenal insufficiency is more in women & they are more likely to have a polyglandular form.[15] Women represented approximately 60% of the total adrenal insufficiency related patient admissions, which is similar to a Swedish study and may reflect the underlying prevalence of Adrenal Insufficiency in the population.[16] However, the study had no autoimmune hepatitis related CLD. The most common associated laboratory findings in chronic primary adrenal insufficiency are anaemia, hyponatremia, hyperkalaemia and both cortisol & aldosterone deficiency.[17] The study similar to previous one, noted that serum sodium levels below 140 mEq/l are highly correlated with adrenal insufficiency.[18] Adrenal insufficiency due to autoimmunity may cause severe hyponatremia and hyperkalemia.[19] Studies on Sheehan's syndrome with recurrent hyponatremia showed that cortisol deficiency causes anaemia.[20] Based on the lab investigations, in patients with RAI, albumin level was low and International normalised ratio (INR) was increased.

These values were statistically significant and indicate that AI in stable cirrhotic patients is related to severity of liver disease.[21] The short corticotropin SST, using 250 µg of synthetic adrenocorticotropic hormone, is regarded as the definitive diagnostic test for adrenal insufficiency in critically ill patients.[22] Authors found a relationship between the severity of liver disease and prevalence of adrenal insufficiency and response to SST which is parallel to severity of cirrhosis assessed by MELD score and CTP score. The study shows that adrenal insufficiency was identified commonly by low peak total cortisol level followed by low delta cortisol level and low total cortisol which is in concordance with previous studies.[23] AI appeared in 65.9% of CTP Class C patients which was in concordance with a study which found that RAI prevalence increases across Child Pugh Classification.[24]

The most significant substrate for steroidogenesis is the amount of cholesterol bound to HDL. In cirrhosis, there is a decrease in HDL concentrations, which is correlated with the severity of liver disease.[25] In the current study it is observed that, as the severity of liver disease increases, HDL level decreases which is in concordance with the

previous studies. It has also been demonstrated that low HDL concentrations are associated with adrenal dysfunction in liver disease patients receiving acute care.[26] To sum up our study, adrenal insufficiency was common even in cases of stable cirrhosis; exclusively correlated with the severity of liver disease and unrelated to the cause of cirrhosis. This study shares some insights on the magnitude of prevalence of Adrenal insufficiency in stable cirrhosis and could potentially guide us to the next step of treating this disorder. The study may have a limitation due to the small number of patients (n=100) and absence of follow up after treatment of AI.

This study has some limitations such as small sample size, absence of follow up and no evaluation of corticosteroid-binding globulin level. The detection of free cortisol is not employed in general practice due to its complexity and high cost.

CONCLUSION

Adrenal insufficiency is more common in patients with chronic liver disease even in non-critically ill patients and in those with low HDL. Prevalence of low HDL and adrenal insufficiency rises with the severity of liver disease which can be determined by peak and delta cortisol levels. While there is no independent predictor for Adrenal insufficiency, it has been found to be solely linked to the severity of liver disease.

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