ORIGINAL ARTICLE

Adrenal Insufficiency in Chronic Liver Disease Patients and its Correlation with Child-Pugh Score

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Abstract

Background: Liver is a storehouse for precursors of all adrenal hormones as well as cortisol binding globulin (CBG). Hence, adrenal dysfunction has been reported in patients with liver diseases. Adrenal Insufficieny (AI) may occur in compensated and decompensated cirrhosis without sepsis or in early and late stages after liver transplantation (LT). In cirrhotic patients, there is low HDL, favouring adrenal insufficiency in conditions of stress.

Methology: This was a cross-sectional, observational study. 60 patients of chronic liver disease admitted to Dr Ram Manohar Lohia Hospital, Delhi and 30 as control were included in study. Patient's blood was collected in fasting state at 8 AM to measure total baseline serum cortisol. ACTH stimulation was done by injecting 250 mcg ACTH intramuscularly. Another sample was collected after 60 min. Samples were centrifuged to collect serum. Total cortisol levels were measured in both the serum samples using chemiluminiscence based method on fully automatic immunoassay analyser.

Results: Mean age in cases was 44.77 ± 7.93 years and mean age in controls was 42.77 ± 5.76 years. Adrenal insufficiency (AI) was present in 24 (40%) patients with chronic liver disease with a statistically significant P value of 0.029. Out of these, 13.33% (2 patients) with Child-Pugh class A, 40% (8 patients) with Child-Pugh class B, and 56% (14 patients) with Child-Pugh class C had adrenal insufficiency. None of the controls showed features of adrenal insufficiency. Patients with AI had a median serum bilirubin level of 2.6 mg/dl with IQR 1.45 - 15.30 compared to median 2.15 mg/dl with IQR 1.4 - 2.95 in those without AI. ROC curve showed that the Child Pugh score may be a good predictor for AI in liver cirrhosis patients.

Conclusion: Adenal insufficiency (AI) forms an important part of the spectrum of chronic liver disease. Deterioration in functions of liver predicts presence of AI, and these patients should be evaluated for adrenal dysfunction periodically. Adrenal function worsens with progression of liver disease.

Keywords: Chronic liver disease, adrenal insufficiency.

Introduction

Liver diseases are common all over the world (prevalence being 4% - 17.5%) as well as in India and the prevalence of liver diseases is likely to increase in the future[1]. Liver diseases have been shown to be associated with various endocrine disturbances[2]. Liver is a storehouse for precursors of all adrenal hormones as well as cortisol binding globulin (CBG). Hence, adrenal dysfunction has been reported in patients with liver diseases[3]. Relative adrenal insufficiency (RAI) is the term given to inadequate production of cortisol with respect to the severity of adrenal insufficiency in cirrhosis[4,5]. More recently, another term, namely critical illness related corticosteroid insufficiency (CIRCI) defined as "inadequate cellular corticosteroid activity for the severity of the patient's illness"[6], has been used. It is proposed that adrenal insufficiency is common in cirrhotic patients too[7,8]. Furthermore, Adrenal Insufficieny (AI) may occur in compensated and decompensated cirrhosis without sepsis[9] or post-liver transplantation (LT)[10]. Mechanisms of adrenal insufficiency in cirrhotic patients are not entirely known, but they may include impaired synthesis in total cholesterol, HDL cholesterol and LDL cholesterol, as well as increased levels of proinflammatory cytokines and circulating endotoxins[11]. Approximately 80% of circulating cortisol is synthesized both at rest and during stress from plasma cholesterol. In cirrhotic patients there is low HDL, favouring adrenal insufficiency in conditions of stress. The effects of corticosteroid therapy in patients with decompensated cirrhosis are controversial[12].

Material and methods

This was a cross-sectional, observational study. 60 patients of chronic liver disease admitted to Dr RML Hospital, Delhi and 30, as controls were included in study.

Inclusion criteria: Patients of age > 18 years, of either sex with evidence of chronic liver disease .

Exclusion criteria: Primary adrenal insufficiency,

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disseminated tuberculosis, sepsis, pregnant females, patients receiving steroid therapy (last dose of steroid received in last 3 months), patients consuming alcohol in last three months.

Methodology

Patients with clinical features suggestive of chronic liver disease were diagnosed on the basis of deranged liver functions of > 6 months duration and/or evidence of chronic liver disease, portal hypertension on radiological imaging and/or evidence of oesophageal varices on upper gastro intestinal endoscopy. All patients underwent a detailed clinical examination at admission. Relevant history and physical examination including symptoms and signs of liver failure, hepatomegaly, splenomegaly and abdominal vein collaterals were recorded. Ascites was graded as none, easily controlled by medications or poorly controlled. Hepatic encephalopathy was graded from 0 to IV. Diagnosis of cirrhosis was based on clinical, biochemical and ultrasonographic findings. Haematological and biochemical workup included measurement of haemoglobin, total leucocyte count, platelet count, prothrombin time, and serum concentration of bilirubin (total and conjugated), protein, albumin, alanine aminotransferase and aspartate aminotransferase. For each patient a Child-Pugh score was calculated[13]. All patients underwent ultrasonography after overnight fast and the following details were recorded: Maximum vertical span of liver; nodularity of liver surface; spleen size (length of its longest axis); diameter of portal and splenic veins; presence of portal-systemic collaterals; and presence of ascites. All patients underwent upper gastrointestinal endoscopy for assessment of oesophageal and gastric varices. Patient's blood was collected in fasting state at 8 AM to measure total baseline serum cortisol. ACTH stimulation was done by injecting 250 mcg ACTH intramuscularly. Another sample was collected after 60 min. Samples were centrifuged to collect serum. Total cortisol levels were measured in both the serum samples using chemiluminiscence based method on fully automatic Immunoassay analyser. Normal range of kit used was 123 - 623 nmol/l. Cut-off level to define adrenal insufficiency was baseline total serum cortisol < 276 nmol/l or peak cortisol levels < 500 nmol/l or delta cortisol (defined as difference between peak and basal cortisol) < 250 nmol/l[6]. Readings were compared with that of control group in which only total baseline serum cortisol levels were measured.

Statistical analysis: Categorical variables were presented in number and percentage (%) and continuous variables was presented as mean ± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected, then non-parametric test was used.

Statistical tests were applied as follows:-

- Quantitative variables were compared using Independent T-test/Mann Whitney test (for nonparametric data) between two groups.

- Qualitative variables were compared using Chi-Square test /Fisher's exact test.

- Logistic regression was performed to find out predictor of adrenal insufficiency taking adrenal insufficiency as dependent variable.

- ROC curve was used to find out cut-off value of Billirubin and Child Pugh score.

A p value of < 0.05 was considered statistically significant.

The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

Results

A total of 60 patients with chronic liver disease were enrolled in this study and 30 age and sex-matched healthy controls were enrolled.

I. Patient characteristics: Cases had a mean age of 44.77 ± 7.93 years and controls had a mean age of 42.77 ± 5.76 years. There was no significant difference between age of cases and controls. Out of 60 patients in case group, 54 (90%) were males and 6 (10%) were females. Out of 30 persons in control group, 27 (90%) were males and 3 (10%) were females.

II. Relation between significant predictors and adrenal insufficiency.

Table I: Adrenal insufficiency: Distribution.

		Child-Pugh class			Total	P value
		A	B	C		
Adrenal Insufficiency	Absent	13 (86.67%)	12 (60%)	11 (44%)	36 (60%)	0.029
	Present	2 (13.33%)	8 (40%)	14 (56%)	24 (40%)	
Total		15 (100%)	20 (100%)	25 (100%)	60 (100%)	

Thus, this study shows that adrenal insufficiency was present in 24(40%) patients with chronic liver disease with a statistically significant P value of 0.029. Out of these, 13.33% (2 patients) with Child-Pugh class A, 40% (8 patients) with Child-Pugh class B, and 56% (14 patients) with Child-Pugh class C had adrenal insufficiency. None of the controls showed features of adrenal insufficiency.
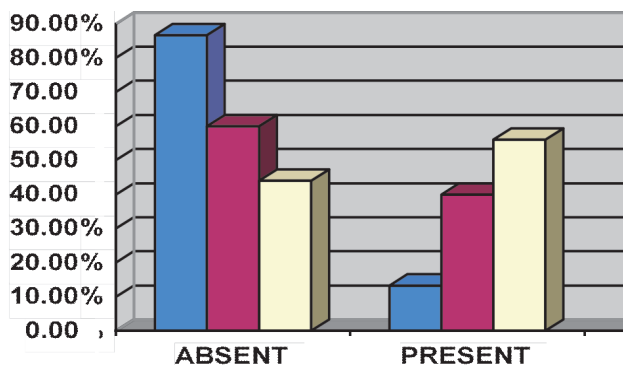
Fig. 1: *Adrenal insufficiency in Child-Pugh class.*

Table II: Bilirubin among study groups.

	Cases			Controls			P value
	Median	Minimum Maximum	Inter Quartile Range	Median	Minimum Maximum	Inter Quartile Range	
Bilirubin (mg/dl)	2.25	0.30 - 27	1.400 - 3.600	0.7	0.4 - 1.1	0.6 - 0.9	< .0005

Thus, bilirubin was significantly higher in cases with a median of 2.25 mg/dl as compared to controls with a median of 0.7 mg/dl.

Table III: Bilirubin, urea and, lipid profile and adrenal insufficiency.

	Adrenal Insufficiency Absent			Adrenal Insufficiency Present			P value
	Median	Minimum Maximum	Inter-Quartile Range	Median	Minimum Maximum	Inter-Quartile Range	
Bilirubin (mg/dl)	2.15	4-5.1	1.4 - 2.95	2.6	0.3 - 27	1.45 - 15.3	.047
S.creatinine (mg/dl)	0.65	0.4- 1.4	0.5 - 1	2.7	0.6 - 3.7	1.65 - 3.1	< .0005
Total cholestrol (mg/dl)	147.5	88 - 189	132 - 158.5	115.5	79 - 150	90.5 - 128	< .0005
HDL (mg/dl)	38	24 - 63	33 - 53.5	26.5	15 - 38	20 - 30	<.0005
LDL (mg/dl)	72.5	39 - 110	50 - 98	37.5	30 - 84	33.5 - 43.5	< .0005

Thus, on evaluating the serum bilirubin level, this study found that there was a significant correlation relation between AI and bilirubin. Patients with AI had a median serum bilirubin level of 2.6 mg/dl with IQR 1.45 - 15.30 compared to median 2.15 mg/dl with IQR 1.4 - 2.95 in those without AI with statistically significant P value of 0.047. There was a highly statistically significant correlation between serum creatinine level and AI, as the 24 patients

diagnosed to have AI, had a median serum creatinine level of 2.70 mg/dl while the other 36 patients who did not have AI, had a median serum creatinine level of 0.65 mg/dl, with a P value of < 0.0005. Thus, this study reveals that patients with adrenal insufficiency had statistically significantly lower values of total cholesterol, HDL and LDL as compared to patients without adrenal insufficiency.

Table IV: AST and ALT among study groups.

	Case	Control	P value
	Mean ± St dev	Mean ± St dev	
ALT (U/L)	54.2 ± 26.41	24.73 ± 6.72	<.0005
AST (U/L)	53.07 ± 26.42	24.43 ± 6.61	<.0005

This study showed that AST was significantly higher in cases with a mean of 53.07 U/L as compared to controls with a mean of 24.43 U/L. Similarly, ALT was significantly higher in cases with a mean of 54.20 U/L as compared to controls with a mean of 24.73 U/L.

Table V: AST, ALT, albumin, urea, triglyceride and adrenal insufficiency.

	Adrenal insufficiency absent	Adrenal insufficiency present	P value
	Mean ± Stdev	Mean ± Stdev	
AST (U/L)	35.03 ± 12.38	80.12 ± 16.86	< .0005
ALT (U/L)	36.31 ± 13.57	81.04 ± 15.98	< .0005
Urea (mg/dl)	30.81 ± 9.03	46.5 ± 13.27	< .0005
Albumin (g/dl)	2.98 ± 0.64	2.5 ± 0.58	< .0005
Triglyceride (mg/dl)	118.92 ± 24.14	86.88 ± 22.49	< .0005

Thus, it was shown that AST was significantly higher in patients with adrenal insufficiency with a mean value of 80.12 ± 16.86 U/L as compared to patients without adrenal insufficiency with a mean of 35.03 ± 12.38 U/L. Similarly, ALT was significantly higher in patients with adrenal insufficiency with a mean value of 81.04 ± 15.98 U/L as compared to patients without adrenal insufficiency with a mean of 36.31 ± 13.57 U/L. The 24 patients diagnosed to have AI, had a serum urea level of 46.5±13.27 mg/dl, while the 36 patients who did not have AI, had serum urea level of 30.81 ± 9.03 mg/dl with a statistically significant P value of < 0.0005. On evaluating the relationship between serum albumin level and AI, it was found that the patients diagnosed to have AI, had significantly lower mean serum albumin level of 2.5 ± 0.58 g/dl, while the patients who did not have AI, had mean serum albumin level of 2.98 ± 0.64 g/dl with a P value: 0.005. This study showed that patients with adrenal insufficiency had statistically significantly lower values of serum triglyceride as compared to patients

without adrenal insufficiency.

III. Logistic regression analysis: In statistics, logistic regression is used for prediction of the probability of occurrence of an event by fitting data to logic function, i.e., logistic curve. This study was done to find out the most significant predictor for AI from the obtained data as Child Pugh classification, serum SGOT/AST, serum bilirubin, serum creatinine and serum albumin.

Table VI: Univariate logistic regression with adrenal insufficiency as dependent variable.

	P value	Exp(B)	95% C.I.for EXP(B)		AIC of Reduced Model	BIC of Reduced Model	-2 Log Likelihood of Reduced
			Lower	Upper			Model
Bilirubin	.023	1.331	1.041	1.702	69.474	71.568	67.474
Albumin	.008	.294	.119	.725	51.710	53.804	49.710
Child-pugh score	.010	1.335	1.071	1.664	45.077	47.172	43.077
ALT	.0005	1.145	1.075	1.221	76.405	78.500	74.405
Creatinine	.001	38.277	4.797	305.44	68.719	70.814	66.719

All these data were analysed by the logistic regression analysis and all the above variables were found to be significant predictor for AI with a P value < 0.05.

IV. Receiver operating characteristic (ROC) curve for adrenal insufficiency: ROC curve is a graphical plot of sensitivity by plotting the fraction of true positives out of the positives (TPR = true positive rates) versus the fraction of false positives out of the negatives (FNR = false negative rate), in other words sensitivity versus specificity.

Table VII: ROC curve for adrenal insufficiency.

	Area under the ROC curve	95% confidence interval	Significance P (Area = 0.5)	Youden index J	Cut-off level	Sensitivity	Specificity
Bilirubin	0.652199	0.518227 to 0.770590	0.059	0.4583	> 5.1	45.83%	100.00%
CPS	0.713542	0.582242 to 0.822894	0.0014	0.4861	> 8	87.50%	61.11%

ROC curve showed that the Child-Pugh score may be a good predictor for AI in liver cirrhosis patients. The area under the Child-Pugh score curve was 0.714 and a Child-Pugh cut-off score of 8 had a sensitivity of 87.50% and specificity of 61.11%. Child-Pugh score could be a good predictor with a considerable sensitivity and specificity as, with high score values, the specificity in detecting AI increased.
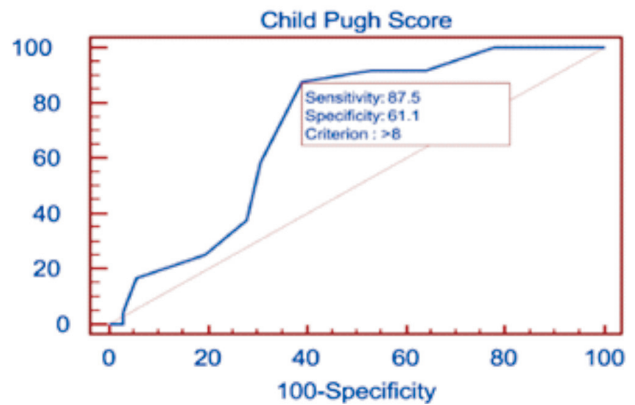

Fig. 3: ROC curve for adrenal insufficiency.

ROC curve showed that the serum bilirubin may be a good predictor for AI in liver cirrhosis patients, as the area under the curve of bilirubin was 0.652. With a serum bilirubin cut-off level of 5.10 mg/dl a sensitivity of 45.83% and specificity of 100% were shown.
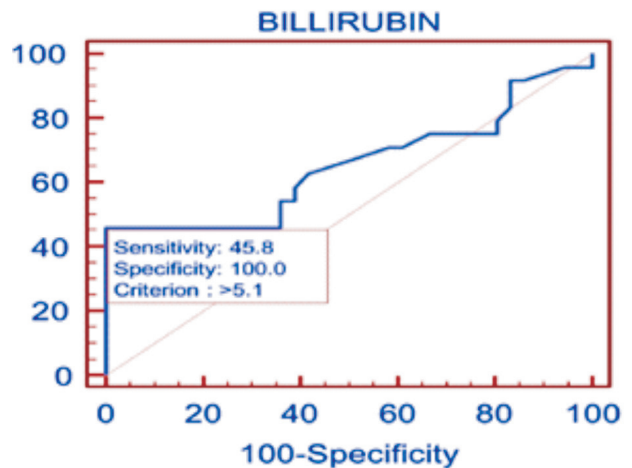

Fig. 4: ROC curve for adrenal insufficiency.

Discussion

60 patients of chronic liver disease were enrolled in this study with a mean age of presentation 44.77 ± 7.93 years (range 21 - 70 years). 90% patients (54 patients) were male and 10% patients (6 patients) were female. Similarly, 30 controls were enrolled with a mean age of presentation 42.77 ± 5.76 years. 90% controls (27 controls) were male and 10% controls (3 controls) were female. This study revealed, firstly, high percentage of adrenal insufficiency in chronic liver disease patients. Secondly, there was increase in percentage of subjects with adrenal dysfunction with progression of liver disease as assessed by Child-Pugh scoring. And lastly, various parameters related to liver dysfunction were also predictors of AI.

In this study, 40% patients (24 patients) with CLD had adrenal insufficiency. Out of these, 13.33% (2 patients) with Child-Pugh class A, 40% (8 patients) with Child-Pugh class B, and 56% (14 patients) with Child-Pugh class C had adrenal insufficiency. Various authors have reported percentage of AI ranging from 33 - 68% in patients with CLD[8]. This is due to varied aetiology, severity and different methods used for the diagnosis of AI in different studies. Galbois et al[14] and Tan et al[15], noted AI in 33% and 39% of subjects with stable cirrhosis with the same method and criteria as in the present study. Fernandez J[8] prospectively evaluated the effects of steroids on shock resolution and hospital survival in a series of 25 consecutive patients with cirrhosis and septic shock. It was found that adrenal dysfunction was frequent in patients with advanced cirrhosis (Child C: 76% versus Child B: 25%, P = 0.08) and resolution of septic shock (96% versus 58%, P = 0.001), survival in the intensive care unit (68% vs. 38%, P = 0.03), and hospital survival (64% versus 32%, P = 0.003) were significantly higher in those who received corticosteroid. Regarding serum creatinine level, this study found that patients with AI had a median serum creatinine level of 2.7 mg/dl with inter quartile range (IQR) 1.65 - 3.10, compared to median of 0.65 mg/dl with IQR 0.5 - 1.0 in patients without AI, with a statistically significant P value of < 0.0005. These findings are in agreement with Tsai et al[16], who found that patients with AI had mean serum creatinine level of 3.2 ± 2.7 mg/dl and in patients without AI the mean was 1.9 ± 1.6 mg/dl which showed statistically significant P value: 0.004. On evaluating the serum bilirubin level, this study found that there was a significant correlation between AI and bilirubin. Patients with AI had a median serum bilirubin level of 2.6 mg/dl with IQR 1.45 - 15.30 compared to median 2.15 mg/dl with IQR 1.4 - 2.95 in those without AI with statistically significant P value of 0.047. This is in agreement with Tsai et al[16], who found a significant relation between AI and serum bilirubin P < 0.001. ROC curve analysis was done and showed that serum bilirubin may be a good predictor for AI in liver cirrhosis patients, as the area under the curve of bilirubin was 0.652. With a serum bilirubin cut-off level of 5.10 mg/dl a sensitivity of 45.83% and specificity of 100% were shown.

This is in agreement with Tsai et al[8], who reported that serum bilirubin was an independent factor in predicting adrenal insufficiency in critically ill patients with cirrhosis and severe sepsis.

The significantly low serum HDL levels (median = 38 mg/dl), serum LDL (median = 72.5 mg/dl), total cholesterol (median = 147.5 mg/dl) and triglyceride (mean = 118.92 mg/dl) in adrenal insufficiency observed in this study further support the notion that liver disease may lead to impaired cortisol synthesis. In a study by Paul E Marik[6], they found the HDL level at the time of adrenal testing was the only variable predictive of adrenal insufficiency (p < 0.0001). This can either be explained by direct decrease in substrate supply[17] or indirect effect of cytokines[11]. The adrenal gland does not store cortisol, increased secretion arises due to increased synthesis under the control of adrenocorticotropin. Cholesterol is the principal precursor for steroid biosynthesis in steroidogenic tissue. At rest and during stress, about 80% of circulating cortisol is derived from plasma cholesterol, the remaining 20% being synthesised in situ from acetate and other precursors. Experimental studies suggest that HDL is the preferred lipoprotein source of steroidogenic substrate in the adrenal gland. Cicognani et al[18] demonstrated a striking decrease in the level of serum HDL in patients with cirrhosis that was related to the severity of disease (Child class).

Conclusion

Adenal insufficiency (AI) forms an important part of the spectrum of chronic liver disease. Deterioration of functions of liver disease predicts presence of AI, and these patients should be evaluated for adrenal dysfunction periodically. Adrenal function worsens with progression of liver disease.

Steroid replacement in CLD patients at time of stress and critical illness may be beneficial as supported by studies of Marik et al[7] and Fernandez et al[8]. They showed that steroid replacement in patients of CLD with adrenal insufficiency leads to resolution of septic shock, decreased doses of vasopressor, increased survival in intensive care and increased hospital survival. Also, presence of AI may predict survival of CLD patients.

Larger studies are needed to establish role of steroids in improving outcome of liver disease patients, also standardisation of criteria for diagnosis of AI in setting of liver disease needs to be established.

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