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Clinical analysis of patients of cirrhosis complicated with adrenal insufficiency

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Abstract. – OBJECTIVE: To evaluate the level of cortisol and adrenocorticotrophic hormone (ACTH) in patients with cirrhosis and to investigate the clinical significance and characteristics of cirrhosis with adrenal insufficiency (AI).

PATIENTS AND METHODS: A total of 118 patients that were hospitalized in the Department of Gastroenterology of Xiangyang Hospital affiliated to Hubei University due to cirrhosis were selected and chemiluminescence assay was used to measure the basal level of cortisol and ACTH in their blood. All the 118 patients with cirrhosis were divided into two groups, cirrhosis with AI group and cirrhosis without AI group and comparison and analysis of the clinical characteristics and prognosis of the two groups were undertaken. About 39 patients with gastrointestinal polyps were used as control group.

RESULTS: The basal level of cortisol of the patient group 329.67±136.1 nmol/l was significantly lower than that of the normal control 460.7±165.48 nmol/l ($p<0.05$). Of the 118 patients with cirrhosis, 32 patients had AI (32/118). Compared with the cirrhosis without AI group, cirrhosis with AI group had significantly increased spontaneous bacterial peritonitis (SBP), Child classes, Child scores, MELD scores and case fatality and the difference was statistically significant ($p<0.05$). The level of albumin and high-density lipoprotein-cholesterol (HDL-C) in 32 patients with cirrhosis and AI was significantly reduced and the prevalence rate of facial pigmentation and ascites were significantly higher ($p<0.05$). But, there was no statistically significant difference between cirrhosis with AI and cirrhosis without AI ($p>0.05$) in other clinical characteristics and laboratory parameters studied.

CONCLUSIONS: The basal level of cortisol in patients with cirrhosis was significantly reduced and about 27% of cirrhosis patients had AI. Patients of the later kind had a higher prevalence rate of SBP, worse hepatic impairment and higher mortality, thus resulting in poor prognosis.

Key Words

Cirrhosis, Adrenocortical insufficiency, Cortisol, Adrenocorticotrophic hormone.

Introduction

Cirrhosis is a common disease that affects the whole body system. Especially when cirrhosis is in decompensated period, it would be accompanied with various complications[1-3]. Recent investigations have shown that cirrhosis would also lead to adrenal insufficiency (AI). Some studies even put forward the concept of "liver-adrenogenital syndrome". Till now, its exact pathogenesis is still unknown. Clinicians are still lacking understanding about this illness[4]. It was hinted from reports that AI would affect the liver function of the patients and, thereby, increase mortality and seriously affect prognosis. Hence in the current study, we have collected 118 patients with decompensated liver cirrhosis who visited the Gastroenterology Department of Xiangyang Hospital Affiliated to Hubei University and attempted an analysis on their adrenal cortex functional reserve and have discussed the clinical significance of liver cirrhosis with AI, classification of liver function and prognosis[5-7].

Patients and Methods

Patients

A total of 150 patients, that were confirmed with liver cirrhosis and were hospitalized from December 2010 to July 2011 in the Department of Gastroenterology of the First People's Hospital of Xiangyang Hubei province, were collected. Of these 150, 32 patients were excluded due to various reasons including severe cardiopulmonary and kidney disease, patients that had taken glucocorticoid not long ago, lack of follow up and no data available concerning their disease. Finally, we had 118 patients that satisfied the standard requirements for the study. In the meanwhile, we also selected 30 patients with inflammatory gastrointe-

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stinal tract polyp from the Department of Gastroenterology of our hospital as a non-cirrhotic control group. Among the 30 patients were 10 patients with gastric polyps and 20 patients with colorectal polyps. To compare the clinical characteristics, basal cortisol and ACTH levels between the cirrhosis group and the control group were studied. Then, the 118 patients in cirrhosis group were divided into cirrhosis with AI group and cirrhosis without AI group according to criteria and compared their differences in terms of clinical information, the severity of liver function and follow-up mortality.

Diagnostic criteria and definition

Diagnosis of cirrhosis: Diagnosis abide by the diagnostic criteria stipulated in Hepatitis B Related Cirrhosis Diagnosis and Treatment Norms Expert Consensus 2014 (Table I). The diagnosis of liver cirrhosis should be based on the clinical manifestations, and examinations, including laboratory examination, histological examination, imaging examination and other examinations. The determination of liver stiffness can be used as a reference for the diagnosis of cirrhosis (2b; B). When diagnosis was needed to be clarified, liver biopsy was the gold standard for clinical diagnosis of liver cirrhosis in compensated stage (2b; A)

Definition of adrenal insufficiency (AI): Basal level of cortisol <138 nmol/l or basal ACTH level >46 pg/mL was considered as AI. The basic value was defined according to the concentration of serum index between 8:00 to 9:00 AM[2].

Study design, data collection and analysis

It is a prospective study. Survey and registration form was used to record the patients' clinical information including the general demographics, other comorbidities, clinical performance and related auxiliary examination (all of the collected data came from the result of the first examination after admission).

Venous blood was drawn from the patients in empty stomach at 8 am in the morning after admission, the blood was placed separately in anticoagulant tubes, was sent to endocrine laboratory of our hospital and detection was made through IMMULITE®/IMMULITE 1000 immunoassay analyzer (Siemens, Princeton, NJ, USA) by means of standard chemiluminescence method strictly in accordance with regulations and finally the corresponding data recorded.

Admission time was taken as a start point, and the prognosis (death, survival) of the patients was obtained that satisfied the inclusion criteria through observation during hospitalization and telephone follow-up within three months after discharge. The prognosis of diseases within three months was taken as the endpoint.

Statistical Analysis

SPSS16.0 (SPSS Inc., Chicago, IL, USA) software was applied for data analysis. Symmetrically distributed measurement data was presented by mean ± standard deviation ($x \pm s$), Students t-test was used to compare the mean between the two groups; chi-square (χ^2) was applied to compare the enumeration data and rate between the two groups. $p<0.05$ was considered as statistically significant.

Table I. Evidence-based medicine stage level and evidence.

Clinical parameters	Cirrhosis with AI	Cirrhosis without AI	p
Length of stay	11.91±7.67	9.86±5.54	0.17
Upper gastrointestinal hemorrhage (Yes/Not)	18/14	46/40	0.95
Spontaneous peritonitis (Yes/Not)*	13/19	18/68	0.006
Hepatic encephalopathy (Yes/Not)	12/20	35/51	0.84
Electrolyte disturbance (Yes/Not)*	11/21	34/52	0.79
Child-Pugh class (n)**			
Level A	3	36	
Level B	12	43	0.02
Level C	17	7	
Child-Pugh scores*	9.38±2.14	7.16±1.69	0.001
Meld scores*	9.23±2.14	6.01±4.94	0.03
Follow-up death toll (n)*	18	10	<0.001

*comparison between cirrhosis with AI and cirrhosis without AI, $p<0.05$
**comparison between Child-Pugh level A, Child-Pugh level B and Child=Pugh level C, $p<0.05$

Results

Demographics of patients and controls

Of the 118 patients in cirrhosis group, 73 were males and 45 were females with a male-female ratio of 1.62:1 and the average age of 55.16±14.1 years. Among the 30 patients in the control group, 19 were males and 11 were females with a male-female ratio of 1.72: 1 and the average age of 52.67±15.07 years. Age, gender, and other co-disease when compared between the two groups, no significant difference was observed (p>0.05).

Cortisol and ACTH levels between cirrhosis group and control group

The average value of the basal cortisol in the cirrhosis group was 329.67±136 nmol/l while that in the control group was 460.72±165.48 nmol/l. The former was significantly lower than the later and this difference was statistically significant (p<0.05). The average value of ACTH in the cirrhosis group was 29.96±23.14 pg/mL while that in the control group was 32.03±14.7 pg/mL and this difference was not statistically significant (p>0.05).

Comparison of clinical characteristics of patients between cirrhosis with AI and cirrhosis without AI

The prevalence of SBP, Child-Pugh scores, Meld scores and patients' mortality in cirrhosis with AI group were significantly higher than those in the cirrhosis without AI group and the difference was statistically significant (p<0.05). But other complications including the length of hospital stay, other upper gastrointestinal hemorrhage, hepatic encephalopathy and electrolyte disturbance showed no significant difference when the two groups were compared (p>0.05; Table II).

Liver function tests in cirrhotic patients with AI

The incidence of chronic hepatic face characterized by facial pigmentation and ascites among patients of cirrhosis with AI were significantly higher than those in the cirrhosis without AI (p<0.05). The level of serum albumin in cirrhosis with AI group was lower than that in cirrhosis without -AI group, while the level of total bilirubin in cirrhosis with AI group was higher than that in cirrhosis without AI group (p<0.05). Other parameters such as age, gender, cause of disease and weakness and poor appetite, liver palms, mean arterial pressure were not significantly different between these two groups (p>0.05, Table III).

Blood lipid level in patients with cirrhosis and AI and cirrhosis without AI

The average value of total cholesterol and HDL-C of cirrhosis with AI group were 2.63±1.08 mmol/L and 0.89±0.53 mmol/L respectively, whi-

Table II. Clinical characteristics of patients' of cirrhosis with AI and without AI.

Parameters	Cirrhosis with AI	Cirrhosis without AI	p
Age	55.88±17.07	55.86±13.02	0.99
Gender (M/F)	20/12	51/35	0.34
Weakness (Yes/Not)	19/13	42/44	0.39
Poor appetite (Yes/Not)	20/12	51/35	0.89
Liver palms (Yes/Not)	29/3	70/16	0.26
Spider nevus (Yes/Not)	30/2	76/10	0.54
Facial pigmentation (Yes/Not)*	16/16	18/68	0.008
Ascites (Yes/Not)*	9/23	17/69	<0.001
Mean arterial pressure (mmHg)	91.97±13.35	93.29±13.52	0.64
Albumin (g/dL)*	29.20±6.72	33.65±6.25	0.01
Bilirubin (mg/dL)*	94.29±130.62	35.33±42.73	0.02
ALT (u/l)*	71.38±59.43	51.66±6.67	0.19
AST (u/l)*	112.12±134.43	67.55±78.67	0.85
BUN	7.24±4.28	6.09±2.65	0.08
Serum creatinine	68.84±24.46	66.41±26.82	0.65
Na (mmol/L)	139.64±6.44	141.39±4.43	0.09
K (mmol/L)	3.78±0.69	3.96±0.64	0.18
Cause			
Virus	15	47	0.45
Alcoholic liver	5	9	0.72
Others	12	30	0.31

*comparison between cirrhosis with AI and cirrhosis without AI, p <0.05

Table III. Clinical characteristics of patients' of cirrhosis with AI and without AI.

Parameters	Cirrhosis with AI	Cirrhosis without AI	p
Total triglyceride TG (mmol/L)	0.98±0.44	1.08±0.73	0.46
Total cholesterol TC (mmol/L)*	2.63±1.08	3.85±1.22	0.01
HDL-C (mmol/L)*	0.89±0.53	1.17±0.41	0.03
LDL-C (mmol/L)	2.11±1.08	2.44±2.59	0.33

*Comparison between cirrhosis with AI and cirrhosis without AI, $p < 0.05$

ch were significantly lower than those of the cirrhosis without AI group ($p<0.05$). Total triglyceride and low-density lipoprotein-cholesterol of the cirrhosis with AI group were reduced, but when compared with those of the cirrhosis without AI group the difference had no statistical significance ($p>0.05$, Table IV).

Discussion

As early as 1975, it was discovered that cirrhosis could influence the synthesis of cortisol[6,7], thereby cause metabolic disorders and finally affect adrenal function. Later, it was found that 51% of the patients with chronic liver disease and septicopyemia harbored AI[8]. In 2010, Fede et al[9] had studied the adrenal functions of liver cirrhotic patients and found out that 38% of them inflicted with AI. The later result was consistent with the current study, which showed the basal level of cortisol in the serum of the 118 liver cirrhotic patients as significantly lower than that in the control group without cirrhosis and 32 patients (27.1%) were confirmed to be with AI according to the diagnosis criteria of our laboratory. The result further indicated that adrenocortical disorder was quite common among the liver cirrhotic patients[10]. But the current study also showed that there was no statistical significance between the two groups (Cirrhosis with AI and Cirrhosis without AI) at the level of ACTH. It might be because the reduced amount of cortisol reserves on some patients was not enough to cause significant changes of ACTH[11].

The current study also showed that the prevalence of ascites and SBP on liver cirrhotic patients with AI increased significantly and compared with the liver cirrhotic patients without AI, the level of albumin was lower and level of bilirubin was higher in the subjects. All of the above could influence and accelerate the decline of liver function and significantly improve the Child-Pugh classification, Child-Pugh scores and Meld scores and result in higher mortality ($p<0.01$) as well as worse prognosis. This result was consistent with other published reports[12-14]. Arnaud Galbois et al[15] had made a study on 130 liver cirrhotic patients and found out that ascites and a low level of albumin were major risk factors of AI, that AI was closely related with the severity of liver function and the increase of mortality and that AI would affect the prognosis of liver cirrhotic patients. So, if clinicians could discover AI early and adopt glucocorticoid or artificially synthesized HDL-C, it was possible to improve the patients' symptoms and reduce their complications[16-18].

The current study also showed that when liver cirrhotic patients were complicated by AI, they were more liable to have hepatic face characterized by facial pigmentation. It might be because a low level of cortisol would reduce its feedback inhibition on hypothalamic-pituitary-adrenal axis and the activity of melanocyte stimulating hormone would increase the amount of ACTH. But the appearance of the symptoms, such as fatigue and weakness was not incurred by the adrenal cortex. The differences on arterial pressure, serum sodium, and potassium concentration between cirrhotic patients with AI and cirrhotic patients without AI

Table IV. Comparison of lipid profile between patients of cirrhosis with AI and without AI.

Parameters	Cirrhosis with AI	Cirrhosis without AI	p
Total triglyceride TG (mmol/L)	0.98±0.44	1.08±0.73	0.46
Total cholesterol TC (mmol/L)*	2.63±1.08	3.85±1.22	0.01
HDL-C (mmol/L)*	0.89±0.53	1.17±0.41	0.03
LDL-C (mmol/L)	2.11±1.08	2.44±2.59	0.33

*Comparison between cirrhosis with AI and cirrhosis without AI, $p < 0.05$

showed no statistical significance. Since there was a lack of significant AI signs, we still hold that the complication of AI on liver cirrhotic patients might be a kind of subclinical state[19].

However, there is still a lack of sufficient theories that could prove the pathogenesis of AI on liver cirrhosis. Pathogenesis might be due to: the reduction in synthesis of high-density lipoprotein cholesterol (HDL-C) as reported in previous study that a low level of HDL-C was closely related with the occurrence of AI and it might be because adrenal cortex could not reserve cortisol and a low level of HDL-C would lead to the reduction of the ACTH reaction[20-22]. Yaguchi et al[23] pointed out that cholesterol was a basic precursor for adrenal synthesized steroid hormones, the most important substrate for the production of steroid hormone, and it had also been proven in fundamental researches[24]. The results of the current study also hinted that the total cholesterol and the level of HDL-C in the cirrhotic patients with AI were significantly reduced. So, the possible reason to explain AI in cirrhosis patients is that cholesterol was an important precursor for the synthesis of steroid hormone and a low level of HDL might be one of the factors for AI in cirrhosis[25].

Conclusions

We observed a prevalence of AI in the cirrhotic patients. AI was closely related with the severity of liver function, the increase of patient mortality and affected the synthesis, metabolism and functional reserve of liver and led to poor prognosis. The liver cirrhotic patients with AI were liable to have facial pigmentation, ascites, malnutrition, and spontaneous peritonitis[26]. Besides, the mechanism of liver cirrhosis with AI might be related with the insufficient synthesis of cholesterol, especially HDL-C. The result could provide a broader researching field for improving the treatment of patients.

Conflict of Interests:

The Authors declare that they have no conflict of interests.

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