ORIGINAL ARTICLES—LIVER, PANCREAS, AND BILIARY TRACT

Critical Illness-Related Corticosteroid Insufficiency in Patients With Cirrhosis and Variceal Bleeding

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BACKGROUND & AIMS: Relative adrenal insufficiency (AI) occurs in patients with cirrhosis with sepsis, but not with variceal bleeding. We evaluated adrenal function in cirrhotic patients with and without bleeding. **METHODS:** Twenty cirrhotic patients with variceal bleeding were evaluated using the short synacthen test (SST) and 10 using the low-dose synacthen test (LDSST) followed by SST. The control group included 60 stable cirrhotic patients, assessed by LDSST (n = 50) or SST (n = 10), and 14 healthy volunteers. AI was diagnosed using SST, based on peak cortisol levels ≤18 μg/dL in nonstressed patients or Δmax <9 μg/dL or a total cortisol level <10 μg/dL in stressed patients with variceal bleeding—the current criteria for critical illness-related corticosteroid insufficiency. Using LDSST, diagnosis was based on peak concentrations of cortisol ≤18 μg/dL in nonstressed patients and <25 μg/dL (or Δmax <9 μg/dL) in patients with variceal bleeding. We evaluated patients with levels of serum albumin >2.5 g/dL, to indirectly assess cortisol binding. **RESULTS:** All healthy volunteers had normal results from LDSSTs and SSTs. Patients with variceal bleeding had higher median baseline concentrations of cortisol (15.4 μg/dL) than stable cirrhotic patients (8.7 μg/dL, $P = .001$) or healthy volunteers (10.1 μg/dL, $P = .01$). Patients with variceal bleeding had higher median peak concentrations of cortisol than stable cirrhotic patients (SST results of 32.7 vs 21 μg/dL, $P = .001$; LDSST results of 9.3 vs 8.1 μg/dL; nonsignificant), with no differences in Δmax in either test. These differences were greater with variceal bleeding than in stable cirrhotic patients with AI. Subanalysis of patients with albumin levels >2.5 g/dL did not change these differences. **CONCLUSIONS: Cirrhotic patients with variceal bleeding have AI. Despite higher baseline concentrations of serum cortisol and subnormal Δmax values, they did not have adequate responses to stress, and therefore had critical illness-related corticosteroid insufficiency.**

Keywords: Liver Disease; Varices; Pituitary; Stress.

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Adrenal insufficiency (AI) results from primary or secondary adrenal disease (impairment of the hypothalamic-pituitary axis [HPA][1,2]). During critical illness, HPA dysfunction might be related to decreased production of corticotrophin-releasing, adrenocorticotropic hormone (ACTH) and cortisol, and/or dysfunction of their receptors.[3]

Patients with cirrhosis have many hemodynamic abnormalities that also occur in patients with septic shock or AI.[4,5] Liver failure could contribute to AI by increasing levels of endotoxin[6] and impairing cholesterol synthesis.[7] Bacterial infections that occur in patients with cirrhosis might be related to altered synthesis of adrenal cortisol,[8] and bacterial and viral products that modify glucorticoid tissue sensitivity and activation of peripheral cortisol metabolism. Abnormal ACTH responses, indicating AI, have also been observed in patients without clinical sepsis, so AI could affect other complications, besides septic shock.[9]

Esophageal varices cause approximately 70% of all upper gastrointestinal bleeding episodes in patients with cirrhosis.[10] Although overall mortality has decreased,[11] mortality is still associated with failure to control bleeding and early-stage bleeding.[10,11] Patients with variceal bleeding are often managed in intensive care;[12] and have frequent infections,[13] which might promote bleeding.[10,14–16] Prophylactic antibiotics are standard therapy because they control bleeding and increase survival.[11]

The occurrence of AI in patients with cirrhosis varies among published studies because of different doses of ACTH used to test adrenal function, different definitions, and problems in interpretation of plasma cortisol measurements.[9] In septic patients, peak cortisol levels differ if patients are given 1 μg of ACTH (the low-dose, short synacthen test [LDSST]) or 250 μg of ACTH (conventional dose, short synacthen test [SST]); this results in an increased diagnosis of AI among patients given the lower dose.[17] The LDSST might provide a more physiologically relevant stimulus and have more sensitive detection of subop-

Abbreviations used in this paper: ACTH, adrenocorticotropic hormone; AI, adrenal insufficiency; CBG, cortisol-binding globulin; CIRCI, critical illness-related insufficiency; HPA, hypothalamic-pituitary axis; INR, international normalized ratio; LDSST, low-dose synacthen test; MELD, model of end-stage liver disease; ns, not significant; SST, short synacthen test.

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timal adrenal function.[18–20] The LDSST was found to be more sensitive than the SST[21–23] in identifying patients with AI, based on meta-analysis.[24]

More than 90% of circulating cortisol is bound to cortisol-binding globulin (CBG) and albumin. Hypoalbuminemia or reduced CBG decrease the total fraction bound to cortisol in serum, but do not affect levels of free cortisol. Because levels of CBG and cortisol are reduced in patients with cirrhosis,[25] measurements of total levels of cortisol might not accurately reflect the level of free cortisol (which can be measured in saliva),[26,27] and could lead to overdiagnosis of AI in patients with cirrhosis.[26] Direct measurements of plasma levels of free cortisol[28] reduce the number of patients found to have AI, although a sizeable proportion still have the disorder (12% in a study of 43 patients with stable cirrhosis). The difference between the total and free levels of cortisol is most marked in patients with serum levels of albumin <2.5 g/dL;[3,29,30] this albumin level has been proposed as a cutoff value, to reduce discrepancies in measurements of free and total cortisol.[3]

An international task force[3] uses the term, critical illness-related insufficiency (CIRCI), and defines it as "inadequate cellular corticosteroid activity for the severity of the patient's illness." They state that in stressed patients, AI is best diagnosed by a maximum change in cortisol level (after SST) of <9 μg/dL, or a random total cortisol level <10 μg/dL.[3]

We evaluated CIRCI in a prospective study of patients with variceal bleeding, patients with stable cirrhosis, and healthy volunteers; we also evaluated associations between AI and patient outcomes.

Methods

Patients

We performed a prospective, observational study that was approved by the Local Hospital Ethics committees. Patients were asked for written consent. Patients with a previous history of hypothalamic-pituitary or adrenal disease history (none had this) and those that had been treated in the past 6 months with drugs that inhibit steroidogenesis were excluded. We evaluated 22 consecutive patients with cirrhosis and variceal bleeding. We enrolled 20 patients in the study (2 refused consent); data were compared with that from 74 controls (14 healthy hospital personnel and 60 patients with cirrhosis, admitted consecutively for investigation of liver disease, for liver biopsy analysis, or for ascites).

Plasma expanders and packed red blood cells (PRBC) were used to maintain hemodynamic stability and hemoglobin levels at approximately 8 g/dL; patients were also given antibiotics (intravenous ceftriaxone), lactulose, somatostatin for 5 days, and banding ligation.[11] Patients were screened for infection by analyses of blood and urine samples, ascites cultures, and chest X-ray images. None of the patients had shock.

Patients were given an ACTH stimulation test the morning after admission. The severity of liver disease was assessed based on Child–Pugh class and model of end-stage liver disease (MELD) score. The SST (tetracosactrin 0.25 mg, synacten; Ciba-Geigy, Rueil-Malmaison, France) was performed by giving patients intravenous injections of 250 μg corticotropin. Serum cortisol concentrations were measured at baseline and at 30 and 60 minutes.[31] The LDSST was given, followed by another SST 2 hours later.[31,32] The LDSST was prepared by adding 250 μg synacten to 250 mL saline in a plastic bottle; 1 mL (1 μg of synacten) was injected immediately after baseline levels of cortisol were measured (at 8 AM). Cortisol was assayed again after 30 and 60 minutes,[33] and at the same intervals after patients were given injections of 250 μg corticotrophin.

Cortisol concentrations were measured by electrochemiluminescence immunoassay (Roche Diagnostics GmbH, Mannheim, Germany).

Definitions

Cirrhosis was diagnosed based on histology analysis or compatible clinical, laboratory, and imaging data. Variceal bleeding was diagnosed based on the presence of hematemesis or melena with either a bleeding varix (active bleeding or clot adherent to varix or variceal ulceration) or when there was no other visible lesion based on endoscopic analysis. Severe bleeding was defined as systolic blood pressure <100 mm Hg or Hemoglobin <8 g/L. Peak cortisol was defined as the highest cortisol concentration 30 or 60 minutes after injection of tetracosactrin. The cortisol response (Δmax) was the difference between peak and basal cortisol.

Diagnosis

AI was diagnosed using results from the LDSST, with a peak cutoff level of cortisol ≤18 μg/dL in nonstressed patients and a peak cortisol level of <25 μg/dL or a Δmax <9 μg/dL from baseline for stressed patients (patients with variceal bleeding).[2,34] Using the SST, AI was diagnosed based on a peak cutoff level of cortisol ≤18 μg/dL in nonstressed patients and a Δmax of <9 μg/dL or a random total cortisol level of <10 μg/dL in stressed patients (patients with variceal bleeding), which are the current criteria for CIRCI.[3]

Groups

In patients with variceal bleeding, group 1 was given the SST (n = 10); group 2 was given the LDSST, followed by the SST 2 hours later (n = 10). Group 3 comprised healthy volunteers (n = 14) who were given the LDSST and SST. Group 4 comprised stable patients with cirrhosis who were inpatients at the hospital and all given the LDSST; 10 were Child–Pugh class A, 18 were Child–Pugh class B, and 22 were Child–Pugh class C. Group 5 comprised patients with stable cirrhosis who were inpatients at the hospital and given the SST (n = 10).

Statistical Analysis

Demographics and clinical and laboratory characteristics for each study group are expressed as median and range. All variables were tested for normal distribution using the Kolmogorov–Smirnov test. The Student *t* test was used to compare the means of continuous variables and normally distributed data. Otherwise, the Mann–Whitney *U* test was used. Categorical data were tested using the χ^2 method. Pearson or Spearman (nonnormally distributed data) correlation coefficients were used to compare groups. Risk factors were determined using univariate analysis; variables significant at the 0.1% level were included in the multivariate analysis using multiple logistic stepwise regression. The χ^2 method was used to analyze rates of AI and cortisol concentrations (baseline and after stimulation tests), serum albumin, and other parameters across study groups. All statistical