CORTICOSTEROID TREATMENT IN THE SETTING OF DECOMPENSATED LIVER CIRRHOSIS WITH RELATIVE ADRENAL INSUFFICIENCY: A CASE REPORT AND A BRIEF REVIEW OF THE LITERATURE

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CORTICOSTEROID TREATMENT IN THE SETTING OF DECOMPENSATED LIVER CIRRHOSIS WITH RELATIVE ADRENAL INSUFFICIENCY: A CASE REPORT AND A BRIEF REVIEW OF THE LITERATURE (Abstract): Relative adrenal insufficiency (RAI) is the term used to describe inadequate production or action of glucocorticoids with respect to the severity of the illness. RAI is frequently found in critically ill patients particularly with septic complications and it is also present in both critically ill and stable patients with liver cirrhosis. In the following study a case report of a patient with decompensated cirrhosis and RAI is presented followed by a brief review of the literature. A 65-year-old male with liver cirrhosis of alcoholic etiology was admitted to hospital with bilateral leg edema, ascites, and marked weakness. At admission, his blood pressure was 82/52 mmHg and he had sinus tachycardia of 130/min. Laboratory analysis revealed hyponatremia (122 mmol/L), while ascites fluid analysis showed no infection. During the first 48 hours of hospitalization the patient remained persistently hypotensive despite adequate vascular filling and the addition of noradrenaline. A standard-dose short synacthen test was performed which revealed a poor cortisol response, which is a compatible criterion for the diagnosis of RAI. Intravenous hydrocortisone therapy was initiated, which resulted in a rapid improvement in patient’s general condition, and increase in blood pressure. As the patient became hemodynamically stable without the need of noradrenaline, the hydrocortisone dose was weaned progressively, and he was discharged after 18 days of hospitalization in a stable condition. Keywords: RELATIVE ADRENAL INSUFFICIENCY; LIVER CIRRHOSIS; HEPATO-ADRENAL SYNDROME; CORTISOL.

Relative adrenal insufficiency (RAI) is the term given to inadequate production or action of glucocorticoids with respect to the severity of illness, and it is frequent in critically ill septic patients (1) as well as in both stable and decompensated cirrhosis with or without sepsis (2-5). The term “hepato-adrenal syndrome” defines an adrenal dysfunction in critically ill cirrhotic patients, and suggests that adrenocortical insufficiency may be a feature of liver disease per se, with a different pathogenesis from that occurring in septic shock (4). Only a few studies assessed corticosteroid therapy in critically ill cirrhotic patients with RAI (4,6-8), and the results were...
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mostly controversial. Some studies reported favorable effects (4,6,7), while a randomized control study (8) has shown no benefit. In this paper, we report a case of a patient with decompensated cirrhosis and RAI, with a brief review of the literature.

**CASE REPORT**

A 65-year old male with decompensated liver cirrhosis of alcoholic etiology was referred to our hospital with large ascites (grade 3), bilateral leg edema and marked weakness. He had a long history (25 years) of alcohol abuse, although he denied any alcohol intake during the last year. On examination, the patient presented cutaneous arterial “spider” angiomas, palmar erythema, Dupuytren’s contractures, grade 3 ascites, peripheral edema, gynecomastia, parotid enlargement, peripheral muscle wasting, mild jaundice, hepatomegaly and splenomegaly. His blood pressure was 78/48 mmHg, he had sinus tachycardia (130/min), and an increased respiratory rate (22/min). The digital rectal examination was normal. Laboratory analysis at admission revealed mild macrocytic anemia, leukocytosis with mild eosinophilia, and thrombocytopenia, elevations of AST, ALT and GGT, hyperbilirubinemia, hypocholesterolemia with low HDL- and LDL-cholesterol values, prolonged INR, hypoalbuminemia, electrolyte disturbance (sodium 122 mmol/L, potassium 2.9 mmol/L). The urine culture was negative and a chest X-ray showed no pathological elements. Abdominal ultrasound showed hepatomegaly with cirrhotic characteristics (nodular structure, heterogeneous echotexture, irregular margins), and signs of portal hypertension (enlarged portal vein of 14 mm, slow portal venous flow, enlarged splenic vein of 11 mm, grade 1 splenomegaly) as well as grade 3 ascites. Large-volume paracentesis was performed associated with albumin infusion (8g for every liter of ascitic fluid removed). Ascites fluid analysis showed no infection (< 75 polymorphonuclear cells/mmc). Upper gastrointestinal endoscopy found large esophageal varices. During the first 24 hours of hospitalization, his blood pressure remained low despite vascular filling, and the patient was referred to the intensive care unit where intravenous norepinephrine was added to fluid replacement therapy. However, the blood pressure remained low (80/50 mm Hg), the patient’s general condition deteriorated and he complained of marked muscle weakness and fatigue; consequently, an adrenocortical insufficiency was suspected and in the third day of hospitalization a standard-dose short synacthen test (SD-SST) was performed which showed a poor cortisol response, compatible with the criteria of RAI (baseline serum total cortisol < 15 μg/dL, delta cortisol < 9 μg/dL). Thus, in our patient serum total cortisol levels at baseline and 60 minutes after the corticotropin stimulation were 9.6 and 12.5 μg/dL, respectively, with a delta cortisol value of 2.9 μg/dL.

The patient received hydrocortisone intravenously 50 mg every 6 hours, beginning with the third day of hospitalization, and the blood pressure values as well as the patient’s general condition greatly improved during the following 24 hours. The norepinephrine dose was gradually reduced and in the fifth day of hospitalization the vasoactive treatment was stopped with no significant change on the blood pressure. The hydrocortisone was weaned progressively (50 mg/day) and the patient was discharged after 18 days of hospitalization.
in stable condition on spironolactone and propranolol.

**DISCUSSION**

Over the last two decades, several studies have reported that in critically ill patients with sepsis the adrenal glands respond inappropriately to stimulation, a condition named initially “relative adrenal insufficiency” (RAI). The name was replaced more recently by the term “critical illness related corticosteroid insufficiency” (CIRCI), defined as an “inadequate cellular corticosteroid activity for the severity of the patient’s illness” (9). Both cirrhosis and septic shock share many hemodynamic abnormalities (e.g. hyperdynamic circulatory failure, peripheral vasodilatation, low blood pressure, increased production of proinflammatory cytokines) (10,11) and, consequently, several studies reported that RAI was found in critically ill cirrhotics with or without sepsis (2-4,6,7,12), in patients with stable cirrhosis (3,5,13), and in liver transplant recipients (4,14). The term “hepatoadrenal syndrome”, used for the first time by Marik et al (4) defines adrenal insufficiency in critically ill advanced liver disease with sepsis and/or other complications, suggesting that adrenocortical insufficiency may be a feature of liver disease per se, with a different pathogenesis from that occurring in septic shock.

Mechanisms of RAI in cirrhotic patients remain largely unknown; however, they may include endotoxemia, impaired synthesis in total cholesterol, HDL and LDL, increased levels of proinflammatory cytokines, and “exhaustion” of the adrenal cortex due to the low levels of steroidogenic substrate (total cholesterol, HDL, LDL) (15).

The diagnosis of RAI in cirrhotic patients is based on the laboratory tests. SD-SST measures total serum cortisol at baseline and 60 minutes after intravenous or intramuscular injection of 250 μg of synthetic ACTH [tetracosactrin (synacthen Novartis Pharma AG, Basel, Switzerland) or cosyntropin (cortrosyn, Amphastar Pharmaceuticals, Rancho Cucamonga, CA, United States)]. A basal serum total cortisol level < 5 μg/dL indicates RAI, while a level > 15 μg/dL will rule out RAI (11). In critically ill patients with cirrhosis RAI is defined either by basal serum total cortisol < 15 μg/dL (2,6) or a delta cortisol (difference between basal serum total cortisol and serum total cortisol after stimulation) < 9 μg/dL (2,6,8,12). Other studies used a peak cortisol level (highest serum total cortisol concentration after stimulation) < 18 μg/dL (7) for the definition of RAI. Most of the studies that included critically ill cirrhotic patients used SD-SST for the diagnosis of RAI (2,6,7,12), while only a few performed a low dose-short synacthen test (LD-SST) (3,4) which uses 1 μg of synacthen given intravenously and serum cortisol measured after 30 minutes. Due to the limitations of all available diagnostic tests, SD-SST remains the most used test for the diagnosis of RAI in critically ill cirrhotic patients, while LD-SST seems to be more appropriate in non-critically ill patients with cirrhosis (11).

The data on corticosteroid therapy in critically ill cirrhotic patients and RAI is controversial, some studies reporting favorable results (4,6,7), while others showing no benefits (8). Harry et al (7) retrospectively assessed the effect of hydrocortisone treatment in a case-control study involving two groups of cirrhotic patients with hemodynamic instability and vasoactive treatment. The group that received hydrocortisone treatment (300 mg/daily)
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had a decrease in noradrenaline requirement, but no benefit in survival. Marik et al (4) evaluated the effect of hydrocortisone given intravenously (300 mg/daily) in a group of cirrhotic patients with hemodynamic instability and found that in patients with RAI hydrocortisone therapy was associated with a significantly lower mortality rate and with a significant reduction of the norepinephrine dosage compared with those patients without RAI. Fernandez et al (6) using SD-SST, reported RAI in 17 of 25 cirrhotics with septic shock, and found that patients who received hydrocortisone therapy had higher rates of shock resolution and hospital survival. In a randomized controlled trial, Arabi et al (8) reported that hydrocortisone therapy (50 mg intravenously every six hours until shock resolution) in cirrhotic patients with septic shock was associated with higher rates of shock reversal and significant reduction in vasopressor doses; however, such therapy did not reduce hospital mortality and had higher frequency of shock relapse and gastrointestinal bleeding.

**CONCLUSIONS**

We presented a case of a cirrhotic patient in which RAI was associated with hemodynamic instability and hypotremia. In our case, treatment with corticosteroids was beneficial and allowed reduction of vasopressor dosage. We therefore conclude that RAI should be suspected and SD-SST performed in any patient with decompensated cirrhosis, hypotension refractory to vasopressors and fluid resuscitation, marked muscle weakness and fatigue, hyponatremia and eosinophilia. Once the diagnosis of RAI is established, treatment with intravenous glucocorticoids can be considered for hemodynamically unstable cirrhotic patients with adrenal insufficiency as it is associated with reduction of vasopressor dosage and may improve survival.

**REFERENCES**


TEA DRINKING AND TUBERCULOSIS

Numerous studies showed that tea drinking helps to prevent obesity, cardiovascular diseases, autoimmune diseases, neurodegenerative diseases and tumors. Chinese researchers discovered the negative association between tea drinking and tuberculosis (TB). Tea leaves contain epigallocatechin-3-gallate, a flavonoid which inhibit the bacterial growth and the bacillus survival in macrophages. The increasing tea consumption is associated with a decreased risk of TB. Subjects who consumed 151-300 g tea / month had a lower risk to develop TB than those with a lower intake of tea. The green tea led to the most evident protection against TB, compared to oolong and black tea. Future studies are needed to determine whether drinking tea can be used in the prevention and control of TB (Mengshi Chen; Jing Deng; Wufei Li; Dan Lin; Congxu Su; Mian Wang; Xun Li; Benjamin Kwaku Abuaku; Hongzhuan Tan; Shi Wu Wen. Impact of tea drinking upon tuberculosis: a neglected issue. BMC Public Health 2015;15(515) ).

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