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Relative Adrenal Insufficiency in Cirrhotic Patients

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ABSTRACT: Relative adrenal insufficiency (RAI) was demonstrated in patients with cirrhosis and liver failure. A relationship appears to exist between the severity of the liver disease and the presence of RAI. Neither the mechanism nor the exact prevalence of RAI is fully understood. There is though a hypothesis that low high-density lipoprotein (HDL) levels in this group of patients may be responsible for the insufficiency of cortisol. Several questions also arise about the way and the kind of cortisol (total cortisol, free cortisol, or even salivary cortisol) that should be measured. The presence of RAI in patients with cirrhosis is unquestionable, but still several studies should come up in order to properly define it and fully understand it.

KEYWORDS: cirrhosis, liver failure, adrenal insufficiency, hepatoadrenal syndrome

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Introduction

Adrenal insufficiency (AI) or Addison's disease is caused by the reduced production of glucocorticoid and mineralocorticoid, which can be the result of structural damage of the adrenal cortex.[1] In this case, we refer to primary AI. Secondary AI is caused by reduced secretion of adrenocorticotrophic hormone (ACTH), usually because of pituitary tumors, lymphocytic hypophysitis, pituitary apoplexy, head trauma, or after inappropriate withdrawal of glucocorticoid therapy.[2]

Prevalence of AI

Addison's disease is a rare condition, with a prevalence of about 35–140 per million and an annual incidence of about four per million in Western populations.[1,3] The most common cause of Addison's disease in developed countries is autoimmune adrenalitis. This can occur either as isolated autoimmune adrenalitis or as part of the autoimmune polyendocrinopathy syndromes. Moreover, several infective agents such as HIV-1, cytomegalovirus, and fungus (cryptococcosis, histoplasmosis, coccidioidomycosis), mostly in immunosuppressed patients,[2] can affect the adrenal gland, resulting in adrenal failure. Tuberculosis remains the most common cause of Addison's disease worldwide. Adrenoleukodystrophy, which is demyelination of central nervous system caused by the mutation of the ABCD1 gene encoding for the peroxisomal adrenoleukodystrophy protein,[2,4] is an important cause of Addison's disease in men.[1]

Cortisol is a corticosteroid that is secreted from the adrenal gland, and it is essential for the normal functioning of the immune system, maintenance of vascular tone, increase of mean blood pressure, and other cellular functions such as inhibition of production of proinflammatory cytokines, free radicals, and prostaglandins, and inhibition of chemotaxis and adhesion molecule expressions.[5,6] In case of severe sepsis, trauma, or stress, cytokines activate hypothalamic secretion of corticotropin-releasing hormone (CRH). CRH activates the

secretion of ACTH by the pituitary, which acts on the adrenal gland and increases the secretion of cortisol. The increase of corticosteroid levels in various tissues during acute illness is an important protective response.[1,7] Nevertheless, absolute levels of cortisol may be insufficiently raised in septic shock. The response of some patients to supplemental corticosteroids suggests that in some patients, the cortisol response to stress is inadequately low to control an inflammatory situation.[5,8,9] This phenomenon has been termed relative adrenal insufficiency (RAI).

AI is a common situation in critically ill patients. Patients with cirrhosis and liver failure share many similar hemodynamic features with patients diagnosed with septic shock and AI. The literature suggests that hypothalamus–pituitary–adrenal (HPA) dysfunction in patients with liver disease is frequent, during both acute critical illness (eg, sepsis, shock, and variceal bleeding) and stable cirrhosis.[5,10–13] In patients with cirrhosis and liver failure, AI during critical illness is associated with increased mortality,[8,14,15] leading to what is termed hepatoadrenal syndrome.[16] However, there is no current consensus defining AI in liver disease.

Diagnosis of RAI

There are some different diagnostic tests for primary or secondary AI. The value of basal serum cortisol and basal plasma corticotrophin at 8 am can provide useful information. Diagnosis of primary AI was based on the value of morning serum cortisol level. Serum cortisol level higher than 18 μg/dL (500 nmol/L) usually excludes Addison's disease, while a level below 6 μg/dL (165 nmol/L) is suggestive of AI.[1,2,17] However, most patients will need short synacthen test (SST) for confirmation or exclusion of the diagnosis.[1,2] Plasma ACTH should be measured in order to diagnose secondary AI. Also, plasma rennin activity is elevated in Addison's disease.[18]

Diagnosis of RAI becomes possible with the use of the stimulating corticotrophin test, known as SST. The test takes place with an intravenous (IV) dosage of 250 μg synacthen, which is a synthetic analog of ACTH, and the measurement of plasma cortisol before and 60 minutes after the dosage. The levels of cortisol should exceed 18–20 μg/dL. RAI is defined as levels of cortisol before the stimulation <15 μg/dL and/or increase of cortisol level <9 μg/dL. In fact, maximum levels of cortisol should not differ, regardless of dosage of 250, 5, or 1 μg ACTH. A recent meta-analysis of 13 studies[19] indicated that the use of 1 μg ACTH provides a more sensitive indication of adrenal function, for the evaluation of cirrhotic patients without critical illness. So, it seems that 1 μg dose of ACTH is more suitable for the diagnosis in these patients.[20,21] On the other hand, it seems that even the time of the day that the measurement of cortisol takes place differs in cirrhotic patients. They seem to have a slightly different circadian rhythm compared with the healthy population, and the mean time of the cortisol rhythm onset and peak concentration were considerably delayed in cirrhotic patients compared to the healthy volunteers. Thus, it is suggested that 9:30 am is more appropriate for sample testing of cortisol level rather than 8:00 am, which is indicated for the general population.[22]

Physiology and Pathophysiology of RAI

Both liver failure and septic shock are life-threatening conditions with many similarities such as hyperdynamic circulatory failure, low mean arterial pressure, and increased cardiac output. Elevated levels of cytokines such as interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α) can be observed in both conditions.[23,24] Cytokines, however, suppress the HPA axis and GR (glucocorticoid receptor) function. Chronic IL-6 elevation may blunt ACTH release.[25] In addition, TNF-α impairs CRH-stimulated ACTH release,[26,27] leading to inappropriately low ACTH levels and low levels of secreted cortisol. This condition was observed during sepsis,[23,24] and might be responsible for the appearance of RAI in hepatic insufficiency too. Nevertheless, the presence of high rates of RAI in recently transplanted steroid-free immunosuppression patients [highly stressed patients; hypoxic, hypotensive, and with very low levels of high-density lipoprotein (HDL)][28] indicates that there is another mechanism as well.

The conclusion of this study[28] is that maybe the presence of low levels of apoprotein-1 HDL affects the appearance of RAI in patients with liver disease and especially in those with cirrhosis and/or advanced liver failure.

According to laboratory studies, HDL is the desired lipoprotein that is used as a substrate for steroidogenesis in the adrenal gland, which is unable to store free cortisol. It is worth noting that in a vast majority of patients with liver failure, the levels of HDL are low.[29–31] Nevertheless, the relation between hepatic disease and RAI is not fully defined yet; thus, it is an area where more studies should be conducted in order to draw conclusions. The hypothesis for the cause of AI and its appearance at high rates in transplated patients, patients with liver failure and cirrhotic patients without sepsis leads to the use of the term *hepatoadrenal syndrome* for these patients.[28,32]

Discussion and Existing Knowledge of RAI

The exact definition of RAI is still a matter of controversy, even though, taking under consideration all the related studies, RAI was detected in 33% of patients with acute liver insufficiency, in 65% of patients with chronic liver disease and sepsis, and in up to 92% of patients who have undergone transplantation and received steroid-free protocol treatment.[33] Specifically, the percentages of AI in patients with liver disease according to different clinical studies are 66% in patients with acute chronic liver failure, 33% in patients with acute liver disease, and 92% in recently liver transplanted patients.[28] In another study, 62% of patients with acute liver failure without elevated hepatic enzymes or encephalopathy have RAI. The authors of this study interpreted the results assuming that subnormal

adrenal response in liver dysfunction was related to the severity of hepatic and multiple organ insufficiency, independent of the presence of sepsis,[14] in which inadequate response to ACTH and lower levels of expected cortisol are observed.[34,35] According to Tsai et al, 51.4% of cirrhotic patients with severe sepsis have RAI.[8] In this study, there also appears a significantly higher percentage of intrahospital mortality in patients with AI, reaching 80.7%, contrary to 36.7% in patients with hepatic dysfunction without RAI. In another study, 68% of cirrhotic patients with severe sepsis have RAI.[15] In this study, there also appears to be differences in the percentage of RAI associated with the severity of the hepatic dysfunction. So, AI appears in 76% of patients with Child-Pugh score C but only in 25% of patients with Child-Pugh score B.[15] According to another study, 36% of cirrhotic patients without sepsis developed RAI. In a thorough analysis of the subgroups done in this study, it was found that patients in a subgroup in which ascites was controlled with low dose of diuretics, only 11%, had RAI, contrary to a second subgroup, in which patients suffering from hepatorenal syndrome or uncontrolled ascites developed RAI at 50%.[36] However, in all the above studies, cirrhotic patients suffered from sepsis.

Recently, a new study has been published that took place with hemodynamically stable cirrhotic patients. This study of Fede et al[37] included 101 hemodynamically stable cirrhotic patients without infection of whom 38% had AI. In this study, RAI was defined as levels of total cortisol serum <18 μg/dL after 20 minutes and 30 minutes of the dosing of 1 μg synacthen, and free cortisol was also measured for which levels >12 μg/dL indicated normal adrenal function. Analyzing the indexes of severity in patients with and without AI led to the result that patients with RAI had a Child-Pugh score of median value 10, contrary to a median value of 7 in the rest of the patients, and a MELD (Model for End-Stage Liver Disease) score of median value 17, contrary to 12 in the rest of the patients. Also in patients with RAI, median value of albumin was lower compared to that of the rest of the patients, and international normalised ratio (INR) was increased in patients with RAI. The measurement of these values indicates that the appearance of AI in hemodynamically stable cirrhotic patients is related to the severity of the liver disease.

The measurement of the levels of free cortisol in serum for the definition of RAI seems to be important if we take into consideration that 70% of serum cortisol is attached to a corticosteroid binding globulin (CBG), 20% is attached to albumin, and only 10% is active free cortisol. According to this, in cirrhotic patients in whom albumin and CBG is reduced, total cortisol may be reduced, but free cortisol could be normal or even elevated. As a result, in patients with more advanced liver disease and/or low total cortisol level, discrepancy exists between the rates of diagnosis of AI using the total and free cortisol criteria.[38] Thus, in these patients, AI should be confirmed by free cortisol measurement. A suggestion also exists for the use of salivary cortisol as a way of diagnosing AI in cirrhotic patients as it is not related to the patients' hypoalbuminemia.[39] There is also an unclear point about the dose of ACTH that should be used for the SST, whether it should be 1 μg [low-dose SST (LDSST)] or 250 μg. Even though most of the studies have used the 250 μg SST, there is an argument according to which the 1 μg dosage (LDSST) is closer to the normally produced quantity from adrenal glands, and thus is more sensitive.[34,35,40–43] Taking this under consideration, LDSST seems most appropriate to be used for the evaluation of RAI.

Another point that is unclear and should be more thoroughly studied is whether supplementary treatment with hydrocortisone would benefit these patients. Only a few studies are addressing this subject. According to a small uncontrolled study,[15] treatment with low doses of hydrocortisone is associated with an increase in shock reversal and in hospital survival. In controversy, a more recent controlled study indicates that even though favorable effects on hemodynamic parameters were observed initially, hydrocortisone therapy did not reduce mortality and was associated with an increase in adverse effects such as further adrenal suppression, gastrointestinal bleeding, and immunosuppression.[44] A number of questions arise about the treatment of these patients with hydrocortisone. Would this treatment affect the need for albumin treatment in these patients? Would the appearance of hepatorenal syndrome as end-stage complication be reduced? Additionally, we should keep in mind that untreated patients with viral hepatitis and

Table 1. Percentages of RAI in cirrhosis from different studies.

Marik et al[28]	66% of patients with acute on chronic liver failure	33% of patients with acute liver disease	92% in recently liver transplanted patients
Harry et al[14]	62% of patients with acute liver failure		
Tsai et al[8]	51.4% of cirrhotic patients with severe sepsis		
Fernandez et al[15]	68% of cirrhotic patients with severe sepsis	76% of patients with Child-Pugh score C	25% of patients with Child-Pugh score B
Alessandria et al[36]	36% of cirrhotic patients without sepsis	11% of patients suffer from controlled ascites	50% of patients suffer from hepatorenal syndrome or uncontrolled ascites
Fede et al[37]	38% of stable cirrhotic patients without infection		

low or undetected viral load could relapse after the use of hydrocortisone, and thus, parallel antiviral therapy is required. It should be mentioned that no data exist about treatment of RAI with hydrocortisone in patients who suffer from RAI and stable cirrhosis. Should they be treated or should hydrocortisone therapy be administered to patients with cirrhosis and bacterial infection and/or sepsis? Since several questions arise and the subject of RAI in cirrhosis is open, it might be useful to examine all cirrhotic patients for RAI in order to keep in mind the potential of a supplementary treatment with hydrocortisone in case sepsis or septic shock arises.[45]

Conclusion

AI seems to be quite common in patients with liver failure, irrespective of the presence of sepsis, and it is related both with the severity of the hepatic disease[8,15,36] and the hemodynamic instability. AI is also linked to increased mortality in cirrhotic patients.[5,8,14,15] For more accurate conclusions about the diagnosis and prevalence of RAI and the suitable treatment, more studies should be conducted. Appropriate dose of ACTH should be reevaluated, possibly comparing both SST (250 μg) and LDSST (1 μg) or using the second one,[34,35,41–43] obtaining the blood samples at the right time of the day (around 9:30 am) and the most accurate way of measuring the levels of cortisol in order to examine the functionality of the adrenal glands, preferably measuring free cortisol levels instead of total serum cortisol.

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Author Contributions

Conceived the concepts: SNA. Analyzed the data: SNA. Wrote the first draft of the manuscript: SNA. Contributed to the writing of the manuscript: OIG, GSG, TGV. Agree with manuscript results and conclusions: SNA, OIG, GSG, TGV. Jointly developed the structure and arguments for the paper: SNA, OIG, GSG, TGV. Made critical revisions: SNA, OIG, GSG, TGV. All authors reviewed and approved of the final manuscript.

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