ADRENAL INSUFFICIENCY (AI) IN CIRRHOSIS

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ABSTRACT

Adrenal dysfunction or insufficiency (AI) in cirrhosis, also described as hepato-adrenal syndrome, is an only recently recognised entity. It is estimated that at least 10% of patients with compensated cirrhosis and over 30% with decompensated cirrhosis have adrenal insufficiency, defined by an abnormal result in the adrenocorticotropic hormone (ACTH) stimulation test. This could increase the risk of cardiocirculatory compromise, infections, and decompensation in these patients but as yet has to be confirmed. An important problem is that diagnosis of adrenal insufficiency in liver disease is difficult, as symptoms can be subtle and overlap with those due to cirrhosis. Furthermore, laboratory testing and reference standards have not been clearly defined. There is evidence that critically ill patients with cirrhosis and AI have a worsened outcome compared with similar patients that do not have AI. However, there is no clear consensus about diagnosis or treatment, in particular regarding steroid replacement therapy, for AI in patients with cirrhosis.

This review will give a brief overview of AI in patients with liver disease, first describing diagnostic tests for AI without liver disease and subsequently the available tests and their pitfalls in the setting of liver disease. As this clinical entity is increasingly recognised, the focus of research will likely change from prevalence and diagnostic studies to mechanisms and therapy, both of which are not defined at present.

Keywords: Adrenal insufficiency, cirrhosis, hepato-adrenal syndrome, CIRCI, diagnosis

ADRENAL INSUFFICIENCY IN PATIENTS WITHOUT LIVER DISEASE

AI results from a deficient production of hormones secreted by the cortical layer of the adrenal gland. This deficiency can be either primary, related to the adrenal gland itself, secondary, through pituitary disease with decreased production of ACTH or tertiary, due to hypothalamic involvement leading to a disruption in the hypothalamus-pituitary-adrenal (HPA) axis caused by a deficiency in corticotropin releasing hormone (CRH). AI is a rare disease in the Western world with primary AI having an estimated prevalence of 35-60/10^6.

Symptoms depend on the acuity of onset, but chronic AI may be oligosymptomatic with fatigue, lassitude and weight loss. Overt AI may only become apparent through intercurrent illness when activation of the HPA axis fails. This may then lead to an impaired cardiovascular response and increased risk of infection.

A particular entity is the relative adrenal insufficiency described in critically ill patients (Critical Illness-related Corticosteroid Insufficiency – CIRCI), where there is inadequate adrenal cortisol secretion relative to the severity of the illness in patients with evidence of systemic inflammation. This may be through an inability to increase cortisol secretion or possibly through end-organ (tissue) resistance.[1]

Assessment of the HPA Axis

Several investigations are available to test the HPA axis. Basal cortisol levels are measured at 8-9am, a time coinciding with the peak in the diurnal variation in cortisol secretion. Generally, total

plasma cortisol is measured, which is a surrogate marker for free plasma cortisol (the biologically active form) in patients with normal plasma protein synthesis. Values <138nmol/l are highly suggestive of AI, whereas values above 415nmol/l essentially exclude AI.

If basal cortisol levels are low or there is a clinical suspicion of AI, ACTH levels should be measured, again, between 8-9am coinciding with the diurnal peak of secretion. In primary AI these exceed 100pg/ml (22pmol/l), however, normal plasma ACTH values do not rule out mild secondary AI.[2] Therefore, dynamic testing is required to establish the diagnosis of AI.[3]

Stimulation tests involve synthetic ACTH in a high or low dose (HDSST or LDSST) or corticotropin. The insulin-induced hypoglycaemia test (IIT) is now rarely used due to obvious concerns about patient safety when inducing hypoglycaemia.

The high dose SST can be performed any time of the day. Blood samples are taken at baseline and 30-60 minutes after intravenous or intramuscular administration of 250mcg of ACTH 1-24 (Synacthen). Post-stimulation levels of over 550nmol/l exclude primary AI. This test has been criticised for its supraphysiologic stimulation of the HPA axis and the possibility that this dose may stimulate adrenal secretion, resulting in levels above 550nmol/l despite a degree of adrenal insufficiency. The HDSST may be most appropriate in critically ill patients.

The low dose SST (LDSST) has therefore been proposed.[4] Here, a 1mcg dose is given intravenously after obtaining a baseline plasma cortisol sample. Further samples are taken at 20 and 30 minutes. The normal response is a cortisol plasma concentration above 500nmol/l. However, the disadvantage of this test is that it has yet to be validated in acute hypothalamic-pituitary disorders and in the critically ill,[5] and therefore is only most appropriate for non-critically ill patients.

The administration of corticotropin-releasing hormone differentiates primary from secondary AI. In primary AI, the elevated levels of ACTH will rise even further in response, whereas in a pituitary disorder causing secondary AI the low ACTH levels will not respond to CRH. CIRCI is defined as a difference of basal to post-stimulation cortisol levels (delta cortisol) of >250nmol/l (9mcg/dl) after HDSST, or a random total plasma cortisol of <276nmol/l (10 mcg/dl).[1]

Management

Overt adrenal insufficiency requires hormone replacement. This is generally achieved with a short-acting corticosteroid, such as hydrocortisone, taken orally in two to three divided daily doses. Hydrocortisone has some mineralocorticoid activity. Different replacement protocols are available, the most commonly chosen is the twice daily oral hydrocortisone replacement with 2/3 of the dose in the morning (20mg) and 1/3 in the evening (10mg) in an effort to mimic the diurnal variation.

The management of patients with CIRCI is controversial. Current recommendations state that the benefit of treatment with glucocorticoids appears to be limited to patients with vasopressor-dependent septic shock and patients with early severe acute respiratory distress syndrome.[1]

ADRENAL INSUFFICIENCY IN PATIENTS WITH LIVER DISEASE

Diagnosis of AI in patients with liver disease is not a straightforward task. Under normal circumstances cortisol is bound to over 90% by cortisol-binding globulin (CBG) and albumin, while only 10% is unbound (free) and metabolically active.[6] Measurement of cortisol levels in patients with cirrhosis is therefore complicated by decreased protein synthesis (CBG and albumin), and binding (mainly to albumin) thus the measured total cortisol underestimates the free cortisol so that this results in overdiagnosis.[7] In critically ill patients with decreased serum albumin levels, overdiagnosis of AI has been reported[8-9] when using total serum cortisol measurements. This is likely to be due to a decrease in CBG. Not surprisingly, CBG levels were also found to be decreased in patients with cirrhosis, this being worse in patients with decompensated (Child C) disease.[10-11] As serum-free cortisol concentration is expensive and difficult to measure, salivary cortisol has been proposed as a surrogate marker. In non-cirrhotic patients salivary cortisol concentrations were in concordance with free cortisol concentrations, even in patients with hypoalbuminaemia and CBG abnormalities.[12] In patients with cirrhosis, Galbois et al.[13] found a better correlation between salivary cortisol and free cortisol than between total and free cortisol levels. Using total serum cortisol for diagnosis led to overestimation of AI in this study. Similarly, in a study of 125 patients with cirrhosis salivary cortisol and serum free cortisol were also closely correlated (in the whole population, Spearman coefficient at T0: r=0.69; P<0.0001).[14] However, the fact that liver

diseases such as alcoholic liver disease, primary biliary cirrhosis and primary sclerosing cholangitis can lead to salivary gland pathology may complicate this test.

Test interpretation, however, remains controversial. In addition, the spectrum of liver diseases, including their acuity, severity and aetiology is very diverse. Thus, different degrees of neurohormonal activation and levels of circulating endotoxins and inflammatory cytokines exist, which may possibly potentiate the effects of concurrent AI.[15] Overall the available evidence suggests a.) AI is common in patients with acute or chronic liver disease and b.) its prevalence increases with more severe hepatic disease. Clinical symptoms are rarely a guide to diagnosis as they overlap with those of cirrhosis in stable patients and many patients with acute or decompensated liver disease are critically ill. The suggested,[1] most appropriate form of stimulation test for critically ill patients with and without liver disease is the HDSST, measuring the peak but more importantly the change in cortisol concentration (delta cortisol). It is likely that patients with decompensated liver disease also fall into the above category, and their adrenal function should be assessed according to CIRCI criteria. The majority of these patients have evidence of systemic inflammatory response syndrome. To date, there are no clear guidelines for diagnosing AI in patients with stable cirrhosis outside the intensive care setting. Apart from the question concerning which stimulation test to choose, the most accurate test for the measurement of cortisol concentration has yet to be established. Similar to intensive care patients, patients with cirrhosis often have low serum protein levels. Measuring total (protein-bound) cortisol concentration may lead to the over-diagnosis of AI in this setting.[13, 16] Free cortisol concentrations have only rarely been assessed in cirrhosis due to the expense and difficulty in measurement. Several studies have assessed salivary cortisol concentration in comparison with total and/or free cortisol.[13-14] Salivary cortisol may therefore be an appropriate surrogate marker for plasma free cortisol concentration,[12] however, collection may be difficult in the ICU environment and contamination may affect the measurement.

Patients that have adrenal insufficiency or CIRCI overall have a worse prognosis in particularly in the setting of sepsis and septic shock, as discussed below. So far corticosteroid replacement has only been recommended in two critically ill patient groups: those with septic shock, particularly when persistently hypotensive and poorly responsive to fluids and vasopressors, and those with early, severe acute respiratory distress syndrome (ARDS).[1]

AI in Stable or Decompensated Liver Disease

Over the last 20 years, 11 studies have been published looking at the prevalence of AI in these groups as well as the correlation with severity of disease.

McDonald et al.[10] performed both SST and IIT on 38 patients with non-alcoholic liver disease and 40 healthy controls. There was a significant 64% reduction in maximal increments of plasma cortisol after IIT, and a 39% reduction after SST. A negative correlation between peak cortisol response and severity of hepatic dysfunction was also observed.

Ten years later Ziets at al.[17] used the CRH test to assess the HPA axis in 52 patients with cirrhosis. This was abnormal in 58% of patients using a peak cortisol level of <550nmol/l or <250nmol/l increase. Again, HPA dysfunction was more common in more severe liver disease. There was no difference between patients with cirrhosis due to alcohol or viral hepatitis.

A study of 88 patients with cirrhosis found a relatively low prevalence of AI (9%) using salivary cortisol measurements after SST.[13] However, this may have been due to active alcohol consumption in >50% of subjects, as alcohol induces adrenal cortisol production.[18] Peak total, delta total and peak-free plasma cortisol were measured during SST in 43 compensated cirrhotics.[16] The prevalence was higher using CIRCI criteria as opposed to standard criteria (47% vs. 39%), and lowest when peak-free cortisol concentrations were used (12%). Neither CIRCI criteria nor peak-free cortisol concentrations have been validated in this patient group.

We performed LDSST on 101 stable cirrhotics without evidence of infection or haemodynamic compromise.[19] The overall prevalence of AI was 38% with a higher prevalence in more advanced liver disease.

In a study from France, 125 consecutive patients were assessed for AI with SST. Basal and peak total, salivary and free cortisol were measured. AI was found in 7.2% as defined by peak cortisol concentration below 510nmol/l. As about a quarter of these patients were septic, use of CIRCI criteria may have been more appropriate for evaluation of AI. Patients who did fulfill their criteria for AI, however, had more severe liver disease. Both groups had similar basal salivary

and free cortisol concentrations.

Over the last years the increasing interest in AI associated with different stages of cirrhosis has led to several interesting abstracts at the EASL conferences[20-23]. All of these studies assessed CIRCI criteria after a high dose of SST. Acevedo et al.[20] compared 10 patients with compensated with 188 patients with decompensated cirrhosis. RAI was found in 27% using CIRCI criteria, however this was similar between the two groups. There was no significant difference in mortality in patients with and without AI.

The same group measured delta cortisol in 166 patients with advanced cirrhosis after SST.[21] RAI was defined by CIRCI criteria and was associated with more severe circulatory dysfunction, septic shock, more severe infections, lower serum sodium and increased hospital mortality. Delta cortisol levels <250nmol/l and/or peak plasma cortisol was used after SST to establish diagnosis of RAI in 85 patients with cirrhosis and non-infected ascites.[23] AI was present in 39% and associated with a higher mortality (33% vs. 10%).

In a study of 37 patients with cirrhosis and acute variceal haemorrhage, RAI was present in 38% and associated with a higher risk of not controlling bleeding at day 5.[22] Our group[24] compared 20 patients with cirrhosis and variceal haemorrhage to 60 stable cirrhotic patients and 14 healthy volunteers using LDSST and SST for diagnosis of AI. We could not demonstrate a difference of the prevalence of AI between the two groups of cirrhotics using SST. However, when LDSST was used, the prevalence of AI was higher in patients with acute variceal haemorrhage. These patients also had higher basal and peak cortisol concentrations than stable cirrhotics associated with similar delta cortisol levels, suggesting an inadequate adrenal response with respect to the severity of the patients' condition (CIRCI).

AI in Critically Ill Patients with Liver Disease With or Without Sepsis

Two other studies have looked at acutely decompensated, septic patients with cirrhosis and assessed the prevalence of AI in this setting. Tsai et al.[25] performed SST on 101 patients with cirrhosis and severe sepsis. AI was diagnosed on the basis of peak or delta serum cortisol levels (<414nmol/l or <250nmol/l). AI was diagnosed in 52% and was related to severity of liver disease, a lower mean arterial pressure, increased inotropic requirements and increased hospital mortality (81% vs. 38%).

Another study from the same year[26] evaluated a similar patient group and diagnosed AI in 68% with a higher prevalence in more advanced disease (CTP-C 76% vs. CTP-B 25%). Stress doses of hydrocortisone were given to patients with AI (50mg/QID). This group was compared to a selection of patients in whom investigation of adrenal function was not undertaken. Shock resolution and mortality rate was improved in the group of patients receiving hydrocortisone. However, Arabi et al.[27] performed a randomised, double-blind, placebo-controlled trial of low dose hydrocortisone replacement (50mg/QID) in septic patients with cirrhosis. This led to a significant reduction in vasopressor doses and higher rates of shock reversal but no reduction in 28-day mortality. It was also associated with an increase in shock relapse and gastrointestinal bleeding.

In 45 patients with acute liver failure AI was diagnosed in 62% using reference ranges from a healthy population.[28] Delta and peak cortisol values were lower in patients with haemodynamic instability, ventilator dependence and in those who died or required transplantation.

Marik et al.[29] performed LDSST in 340 patients with acute or acutely decompensated liver disease as well as recently or previously transplanted patients admitted to the intensive care unit. AI was found in 33% of patients with fulminant hepatic failure, 66% of patients with acutely decompensated cirrhosis, 61% of patients previously transplanted and in 92% of patients recently transplanted and maintained on steroid-sparing immunosuppressive regimen.

AI in Liver Transplant Recipients

Assessment of adequate adrenal function after liver transplantation is even more complicated by the recent surgery and steroid-containing immunosuppressive regimens. We assessed the intraoperative administration of 1000mg of methylprednisolone in 90 consecutively enrolled patients undergoing first elective liver transplantation, irrespective of adrenal function.[30] Requirements for vasopressors, invasive ventilation, fluid administration, haemofiltration, and length of intensive care stay were all significantly reduced in patients who received the methylprednisolone bolus intraoperatively.

AI has been reported in post-transplant patients

with steroid sparing regimen[31] and after steroid withdrawal.[32] Subclinical/latent adrenal insufficiency may adversely affect outcome in the operative and postoperative liver transplant setting, which maybe complicated by infection, hypotension and severe blood loss. An inadequate adrenal reserve is likely to significantly impair an appropriate stress response in these patients.

SUMMARY AND FUTURE STUDIES

AI is present in at least 10% of patients with cirrhosis, and the prevalence increases with more severe liver disease. The pathophysiology of AI in cirrhosis has yet to be elucidated. In the general population the most common cause for AI is primary adrenal dysfunction (pred. autoimmune adrenalitis). In liver disease however, hypothalamic-pituitary impairment[10] has been suggested as the predominant cause for AI. Possible explanations include the increased concentration of circulating cytokines, which may interfere with appropriate activation of the HPA axis.[33] Other potential causes include the use of CNS depressants, pituitary/adrenal ischaemia or haemorrhage and infections. All of these conditions are known to have an effect on the HPA axis.[34] The potential effect of increased brain water seen in acute and chronic hepatic encephalopathy is also unknown. As far as we are aware, there are no post mortem studies of adrenal or pituitary anatomy and pathology in patients with cirrhosis.

The end-organ effects of latent AI in liver disease are unclear. However, in times of physiologic stress, such as variceal haemorrhage, ascites formation or infection, patients with AI seem to have a worse prognosis. In particular with regards to circulatory dysfunction AI may play an important role in patients with cirrhosis. In an already vasodilated cirrhotic patient, cortisol deficiency may lead to more profound hypotension with detrimental effects on end-organ perfusion, particularly on the kidneys, and response to vasoconstrictors. Currently it is unknown whether AI in cirrhosis has direct effects on cardiac function. However there are similarities between cirrhotic cardiomyopathy (CM) and AI-associated CM, both of which may only become apparent in stressful conditions.[15]

An interesting question is whether treatment for decompensation in these patients should include cortisol replacement and whether decompensation could be delayed or prevented.

In summary, studies are needed to facilitate the diagnosis of AI and a consensus is required to define diagnostic criteria. The effect of AI in compensated and decompensated liver disease, as well as the optimal treatment/replacement strategy for these patients, has to be further assessed in randomised controlled trials.

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