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Hypothalamus-pituitary dysfunction is common in patients with stable cirrhosis and abnormal low dose synacthen test

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ABSTRACT

Background: Adrenal insufficiency is often present in cirrhosis. We hypothesize that a prolonged adrenocorticotropic hormone (ACTH) stimulus can restore cellular capacity of adrenal glands to secrete cortisol. Aim of our study was to assess adrenal responsiveness to prolonged ACTH stimulation in cirrhotics.
Methods: Prospective observational study in 121 consecutively admitted cirrhotic patients undergoing a low dose short synacthen test and plasma ACTH measurement using a chemiluminescence immunoassay. Long synacthen test was performed if the low dose was abnormal.
Results: 46 patients had abnormal low dose short test (38%), and 29 underwent the long test: 41% showed normal response (Group 1), 55% showed delayed response (Group 2) and 1 had abnormal response (4%). Baseline ACTH levels did not significantly differ between the two groups. Median basal cortisol was higher in Group 1 (296 vs. 198 nmol/L; $p = 0.02$). Using ROC curve basal cortisol <254 nmol/L was associated with a delayed long synacthen test response (AUC 0.78, $p = 0.001$) with good accuracy (sensitivity 67%, specificity 81%).
Conclusion: A delayed cortisol response after a prolonged ACTH stimulation is found in over fifty percent of cirrhotics with abnormal low dose short synacthen test, confirming that the mechanism of hypoadrenalism in these patients could be related both to adrenal cellular dysfunction and hypothalamus-pituitary adrenal axis impairment.

1. Introduction

Adrenal insufficiency (AI) is defined by a deficient production or action of glucocorticoids. It can be due to a primary disorder of the adrenal glands resulting in deficiency of cortisol production (primary AI), or to a hypothalamo-pituitary disorder resulting in deficiency of adrenocorticotropic hormone (ACTH) or corticotropin-releasing hormone (CRH) secretion (secondary AI) [1]. Adrenal dysfunction, the so-called "hepato-adrenal syndrome" [2], has been described in patients with liver disease [3], with variable prevalence, according to the particular study population: critically ill patients (33–92%) [2,4–7], stable cirrhosis (31–60%) [8–14] or decompensated cirrhosis [15], such as variceal bleeding (30–48%, according to the 250 or 1 μg synacthen test) [16] and ascites (39%) [17].

The standard diagnostic test for suspected AI has been the rapid ACTH stimulation test, based on the administration of synthetic ACTH 1–24 [18]. The short synacthen test (SST), using 250 μg of cosyntropin (Synacthen®), is currently recommended in critically ill patients [19], whereas the low dose short synacthen test (LDSST), using a more physiological dose of 1 μg of cosyntropin, has been proposed as a more sensitive marker of sub-optimal adrenal function in non-critically ill patients [20]. However, there are no clear recommendations for assessing adrenal function in patients with liver disease [3].

The mechanism leading to adrenal dysfunction in liver disease has not been established, and it is unclear at what level of the hypothalamo-pituitary-adrenal (HPA) axis the damage is located (i.e. primary or secondary AI). The rapid ACTH stimulation test (using 1 μg or 250 μg of cosyntropin), which is the test used in previous studies to assess adrenal dysfunction in patients with cirrhosis [2,4–10,12,16,21,22], is not able to differentiate primary

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from secondary AI. Basal plasma ACTH levels are useful for differentiating primary and secondary forms. In patients with primary AI, plasma ACTH levels are high and usually exceed 200 pg/mL (44 pmol/L). However, the basal ACTH levels must always be interpreted with caution, considering the episodic nature of ACTH secretion and its short plasma half-life [1]. Normal plasma corticotropin values rule out a primary AI, but not a mild secondary AI [23]. Moreover in patients with liver disease ACTH values did not differ between patients with and without adrenal dysfunction [9,12].

The long synacthen test (LST), using 1 mg depot tetracosactrin, is another simple and reproducible test used to diagnose primary AI. Cortisol concentration is measured before, 4, 8 and 24 h after intramuscular injection of 1 mg depot tetracosactrin. In healthy subjects, plasma cortisol levels rise rapidly within the first hours and the value at 24 h shows little further increase. In ACTH-deficient patients with atrophic adrenals, a smaller initial response occurs, with a progressive rise at 24 h. By contrast, in primary hypoadrenalism, there is no response at all because endogenous ACTH levels are already raised [24,25].

The aim of our study was to assess the adrenal responsiveness to prolonged ACTH stimulation in patients with stable cirrhosis, to investigate whether the prolonged stimulation with ACTH is able to restore the capacity of adrenal glands to secrete cortisol. We used a multistep diagnostic approach: the LDSST and basal ACTH measurement were initially performed, and the LST was subsequently carried out to study the adrenal response to prolonged ACTH stimulation.

2. Patients and methods

This was a prospective observational study performed at the Royal Free Sheila Sherlock Liver Centre (London, UK) and at the Garibaldi Hospital's Internal Medicine Department (Catania, IT) between July 2010 and October 2012.

This study was designed and conducted according to the principles of the Declaration of Helsinki and was approved by the local ethics committee, and a written informed consent was obtained from each participant.

2.1. Inclusion criteria

We consecutively enrolled patients with a diagnosis of cirrhosis based on the combination of clinical features, radiological imaging, presence of portal hypertension, compatible biochemical parameters, and/or confirmatory liver biopsy. Patients admitted with decompensated cirrhosis (ascites, variceal bleeding, jaundice, encephalopathy) were enrolled in the study protocol at least 6 weeks after the resolution of the acute episode of decompensation.

Adrenal function was studied in all patients performing the LDSST (First Test), ACTH and CBG measurement. Patients who failed to pass the first test underwent the LST (second test), at least 24 h after the first test.

The primary outcome measures of our study included ACTH values and cortisol levels before, 4, 8 and 24 h after the administration of 1 mg depot tetracosactrin.

2.2. Exclusion criteria

We excluded patients with sepsis or haemodynamic instability (mean arterial pressure <60 mmHg or vasopressor dependency), previous history of HPA axis disease, current or recent (within the previous 3 months) history of corticosteroid therapy or other drugs that could impair the HPA axis, younger than 18 years, and pregnancy.

2.3. Low dose synacthen test

The test was performed between 8.00 and 9.00 AM, following an overnight fast. Blood samples were obtained immediately before, 20 min and 30 min after an intravenous injection of 1 μg of synacthen. Low-dose synacthen was prepared by adding 250 μg of synacthen (1 mL) to 249 mL saline in a plastic bottle; 1 mL of this solution (containing 1 μg of synacthen) was injected immediately, as previously described [26]. For the purpose of this study, AI was defined by a peak total cortisol below 494 nmol/L at 20 or 30 min after stimulation [27]. Moreover in a subset of 25 patients the serum free cortisol was also measured, and a peak free cortisol <33 nmol/L after stimulation defined an impaired free cortisol response [28].

2.4. Long synacthen test

Blood samples were obtained to measure cortisol levels before, 4, 8 and 24 h after intramuscular injection of 1 mg depot tetracosactrin; this generates a supraphysiological ACTH concentration (supramaximal stimulation) for over 24 h. The stimulation of the adrenal over this period tests its mass response, including its ability to synthesize and release cortisol. In health, plasma cortisol will rise to 900 nmol/1 or more by 4–8 h and shows little further increase at 24 h. By contrast, in ACTH-deficient patients with sluggish adrenals, a smaller but progressively incremental response occurs often peaking at 24 h. In primary hypoadrenalism the adrenal glands are partially or completely destroyed and endogenous ACTH levels are already raised, thus plasma cortisol levels will not respond to additional ACTH stimulation and cortisol levels fail to rise, remaining subnormal (below 900 nmol/1) throughout the test [24,25].

2.5. Laboratory measurements

Total cortisol concentrations were measured using an electrochemiluminescence immunoassay on a Roche modular E170 analyser (Roche Diagnostics, Mannheim, Germany); intra-assay CVs <1.8% (assessed at 129 nmol/L, 352 nmol/L and 717 nmol/L); inter-assay CVs <4.0% (assessed at 68 nmol/L, 516 nmol/L and 832 nmol/L). Plasma ACTH concentrations were measured using a chemiluminescence immunoassay on an Immulite 2500 analyser (Siemens Medical Solutions Diagnostics Limited, Llanberis, UK) (intra-assay CVs <4.7%; inter-assay CVs <6.4%). Free Cortisol, assessed in a subset of 25 consecutive patients, was measured at the University Hospital of South Manchester as previously described [29]. Briefly, 0.5 mL samples of serum were centrifuged in Ultrafiltration devices (Amicon Ultra-4 10 kDa; Millipore, Bedford, MA), and free cortisol was measured in the ultrafiltrate by LC–MS/MS.

2.6. Statistical analysis

Data are expressed as means with standard error (SE), frequency (percentage) or medians with interquartile range (IQR) as appropriate. Comparisons between patients with and without adrenal dysfunction were performed using χ^2 test (for categorical variables), Student's *t*-test or the Mann–Whitney *U* test (for continuous variables, as appropriate). Correlation analysis was performed using the Spearman correlation coefficient. All statistical tests were two-tailed, and the significance level was set at $p = 0.05$ or less. All statistical analyses were done using the SPSS 13.0 software for Windows.