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Case Report

Hepato-Adrenal Syndrome: An Underestimated but Challenging Complication of Cirrhosis

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Abstract

Hepato-Adrenal Syndrome is an underdiagnosed condition that is still incompletely understood but appear multifactorial. His prevalence can reach 72% in series of hospitalized patients for cirrhosis. change in protein homeostasis imposed by hypoalbuminemia induced by cirrhosis and the decrease in all globulin binding outside of SHBG tends to cause diagnostic doubts. We report the case of a patient with a viral cirrhosis at the stage of decompensation in whom we diagnosed a hepato-adrenal syndrome suggested by evocative clinical symptoms and associated to a refractory hyponatremia. The spectacular evolution under hydrocortisone led us to reiterate our diagnosis even before performing the adrenal stimulation test. We propose a review of literature that highlights the epidemiological, pathophysiological and diagnostic aspects of this pathological entity.

Keywords: Hepato-Adrenal Syndrome, Cirrhosis-Electrolyte disturbances, hyponatremia, epidemiological, pathophysiological.

INTRODUCTION

The prevalence of adrenal insufficiency in cirrhosis is variable, ranging between 15% and 72%, but this prevalence seems too underestimated due to the methodological constraints related to the diagnosis of causality [1]. Relative adrenal insufficiency was originally described in the critically ill population and is currently termed critical illness-related corticosteroid insufficiency (CIRCI) [1]. Marik *et al.,* first reported the condition in patients with cirrhosis in 2005, for which they chose the name of "hepato-adrenal syndrome" [3]. In practical terms, many authors acknowledge the challenge posed by measuring serum total cortisol (TC) in cirrhosis yet there is insufficient evidence for current guidelines to provide recommendations regarding optimal diagnostic strategies and clinical thresholds [4]. Challenges facing clinicians are many, one of them is the lack of validated cirrhosis-specific and/or hypoproteinemic total cortisol (TC) reference ranges [5]. Another challenge unique to cirrhosis is that the development of AI may be both multifactorial and multilevel [6]. Trying to segregate a specific case into a purely primary or secondary (or tertiary) process may not be easy given clinical heterogeneity. Finally, patients with cirrhosis are at increased risk to develop critical illness and they are most often poly-medicated, which is an established AI risk factor in the general population [7].

CLINICAL CASE

We report the case of a 46-year-old man. His medical history included type 2 diabetes mellitus and chronic hepatitis B infection treated with tenofovir alafenamide. Since September 2025, the patient had been followed for decompensated hepatitis B-related cirrhosis, presenting with diuretic-refractory ascites. This condition led to prolonged hospitalization in order to better manage his advanced liver disease, then classified as Child–Pugh class C (score 11) with a MELD score of 22. At initial clinical assessment, he presented with deep asthenia, severe cachexia, anorexia, tense ascites, bilateral lower limb edema, and ecchymoses, a tendency to low blood pressure but without hepatic encephalopathy.

Laboratory investigations revealed refractory electrolyte disturbances including hyponatremia and hypokalemia; Na+ was ranging between 119 and 124 mEq/L, natriuresis was inadequate for hyponatremia with a Na u = 28 mEq/L of urine. K+ was ranging between 3.0 and 3.2 mEq/L without any obvious urinary loss on the urine electrolytes. We also found normocytic normochromic anemia (hemoglobin 10.4 g/dL), mild

inflammatory syndrome (leukocytosis 15,710/mm³, C-reactive protein 16 mg/L), a severe coagulopathy (prothrombin time 17%, platelets 47,000/mm³), with progressive renal dysfunction Creatinine = 19 mg/L then 21 mg/L. A1C= 7.1%. Given the persistence of refractory hyponatremia, the normalization of glycemic profile, and the tendency to hypotension, an 8-hour serum cortisol was requested; 8H Cortisol= 2.2 ug/dL (60.69 nmol/L). A second confirmatory dosage found 1.9 ug/dL (52.41 nmol/L) thus diagnosing adrenal insufficiency. Further endocrine evaluation demonstrated a hypogonadotropic hypogonadism (testosterone = 1,98 ng/mL with abnormally normal gonadotropin) (and mild hyperprolactinemia (24 ng/mL). SHBG and free testosterone were not requested because they are not available in our hospital. Imaging confirmed cirrhosis with multiple benign nodules (LRADS 2) and large-volume ascites, without evidence of hepatocellular carcinoma. Bone densitometry revealed severe osteoporosis.

A broader pathophysiological interpretation led to the diagnosis of hepato-adrenal syndrome, reflecting an inadequate hypothalamic–pituitary–adrenal axis response in advanced cirrhosis. This condition likely contributed to impaired vascular tone and renal hypoperfusion, thereby explaining the persistence of renal dysfunction, hyponatremia, and diuretic resistance. Our patient was given hydrocortisone and marked a spectacular change both clinically and in ionic parameters

DISCUSSION

Hepato-Adrenal Syndrome: is a really rare condition?

It is surely a pathology that is too under-diagnosed, and this mainly because the symptomatology of adrenal insufficiency made of asthenia and electrolytic problems are indeed common symptoms as well as in cirrhosis. In a meta-analysis that investigated 182 studies, 16 of which met the PRISMA criteria, it was clearly demonstrated that adrenocortical dysfunction is frequent in patients with cirrhosis, even those that are stable [8]. Results showed an overall prevalence of RAI in studied publications about 49.4% (744/1507), with a slightly higher prevalence of 53.6% (516/962) in patients with decompensated cirrhosis (odds ratio [OR] 1.61; 95% CI [1.30–1.99], P\ 0.001) [8-12]. Moreover, the prevalence of RAI was 68.9% (404/586) in critically ill patients with sepsis or septic shock (OR 3.09; 95% CI 2.42–3.94, P\ 0.001), and 41.8% (228/545) in non-critically ill patients with cirrhosis such as compensated cirrhosis [8-12].

In some single-center studies we were able to highlight much greater prevalences, as Mohamed Badr Mohamed *et al.,* who highlighted adrenocortical insufficiency (ACI) in 33 patients out of the 45 patients subjected to his study (73.3%) [13]. In cohort studies, Paul E. Marik *et al.,* conducted a study cohort consisted of 221 patients, of whom 120 (54%) were diagnosed with adrenal insufficiency on initial diagnostic testing and were excluded from further analysis. The remaining 101 patients comprised those who made up the group of interest. On follow-up, 16 (16%) of this developed adrenal failure a mean of 3 days after initial testing [14].

Hepato-Adrenal Syndrome: How do we get there?

From an etiopathogenic point of view, adrenal insufficiency is an underrecognized endocrine dysfunction spanning the spectrum of liver disease. Causal pathways of AI in cirrhosis are still incompletely understood but appear multifactorial. Several theories have been put forward, with a large number of abnormalities that may be reported on several scales of the hypothalamic-pituitary- adrenal axis.

ACTH secretion may play a consequent role; as established Cortisol secretion is non-linear in healthy individuals, oscillating in circadian and ultradian (60- to 90-minute cycles) fashion with an early morning peak and nocturnal nadir [15]. Yet it has been demonstrated disruption of normal circadian rhythm in decompensated cirrhosis, which impacts cortisol secretion [16]. Montagense *et al.,* reported differences in free cortisol secretion rhythm, such that the morning peak was delayed in patients with cirrhosis, particularly those with decompensated disease [16]. Some authors reiterated that delayed peak of free plasma cortisol (FPC); this effect was more pronounced in those with decompensated disease [17].

Metabolism of cortisol is also affected in cirrhosis. Some studies demonstrate that liver disease is associated with reduced 11β-HSD enzyme levels and thus an increase in circulating glucocorticoids [18, 19]. Furthermore, cortisol elimination is impaired in cirrhosis and parallels liver disease severity [5]. Endocrine dysfunction in cirrhosis is also a byproduct of impaired hepatic synthetic function. As long as the liver produces all hormonal binding globulins, thus there is a global decrease (SHBG excepted) in cirrhosis [2].

As for the abnormalities directly affecting adrenal steroidogenesis, the mechanisms are still also poorly understood, but hypothesis tend to incriminate a dyslipidemia pathway. Adrenal steroidogenesis is dependent on hepatic cholesterol trafficking via high-density lipoprotein (HDL). These kind of Lp is principally composed of Apolipoproteins apo-A1. However, it is well-established that apo-A1 and HDL levels correlate with hepatic synthetic function [20]. this mechanism has often been found in clinical studies [14]. Apart from the situation involving dyslipidemia, there are several other hypotheses which tend to explain this causality; Deficient intrinsic adrenal enzymatic activity leading to either excess precursor steroids (in relation to cortisol) or pathway shunting, Altered vascular tone in the setting of splanchnic vasodilation and low effective circulating volume leading to chronic adrenal

hypoperfusion, and Suppressive effects of pro-inflammatory cytokines on HPA axis hormonal secretion [21, 22].

Hepato-Adrenal Syndrome: How to establish it as a diagnosis?

Critical illness is still a real challenge for us clinicians when assessing adrenal functionality. Although critically ill hypoproteinemic patients are expected to have random TC levels > 262 nmol/L, the validity of using baseline and Cosyntropin-stimulated TC levels in this population is questioned (sometimes even controversial) [23]. Some authors found that nearly 40% of critically ill patients with albumin ≤ 2.5 g/dL had peak TC levels < 510 nmol/L despite normal and stimulated FPC levels [24]. We also noted that in the hypoproteinemic subpopulation, basal FPC accounted for 19% to 62% of measured TC [24]. Another big challenge is low CBG levels in patients with cirrhosis and critical illness. Inflammatory states such as sepsis induce conformational change in CBG such that its affinity for cortisol decreases, allowing for molecular uncoupling and enhancing cortisol delivery to tissues [25]. Moreover, the ACTH-cortisol dissociation phenomenon in critical illness demonstrates that despite maximal levels of endogenous cortisol, ACTH levels are frequently lower than required and may reflect suppression of pulsatile ACTH and cortisol secretion [26].

Due to this state of limitations of TC measurement in cirrhosis, the development of binding globulin-independent markers appears to be better adapted to adrenal function assessement ; The CSR max (the peak rate at which the adrenal glands produce cortisol under maximum stimulation) is a good calculated parameter that has been reported in several populations, including cirrhosis, but requires mathematical modeling and is best used for research rather than at bedside [27]. Because FPC is biologically active and unbound to CBG or albumin, some advocate for its use in cirrhosis. Proponents of FPC argue that AI is overdiagnosed in cirrhosis when standard TC thresholds are used to interpret ACTH stimulation testing [2, 28]. In general, an abnormal stimulated TC response in a patient with cirrhosis therefore could represent one of three possibilities:

- Absolute AI: a non-situational reduction in adrenal steroid secretion
- Relative AI: an inadequate adrenal response to stressful stimuli
- False positive: an artifact of decreased hepatic binding globulin synthesis.

Back to our patient, the TC levels at baseline were too low and the response to hydrocortisone served as additional evidence for our diagnosis. We did not indicate a stimulation test in response to the patient's condition deemed serious, and the rest of the stimulation was postponed until the comorbidities had recovered.

CONCLUSION

Hypoalbuminemia and electrolyte disturbances due to low oncotic pressure and the use of diuretics are factors that make the diagnosis of hepato-adrenal syndrome difficult. often requiring multi-disciplinary collaboration between gastroenterologist and endocrinologist.

Abbreviations:

AI: adrenal insufficiency
ACTH: adrenocorticotropine hormone
CBG: cortisol binding globulin
CSR max: maximal cortisol secretion rate
FPC: free plasma cortisol
HAS: hepato adrenal syndrome
HDL: high density lipoprotein
SHBG: sex-hormone binding globulin
TC: total cortisol

REFERENCES

1. Moini M, Yazdani Sarvestani M, Shams M, Nomovi M. Evaluation of adrenal function in nonhospitalized patients with cirrhosis. *Can J Gastroenterol Hepatol* 2017; 2017: 2354253.doi:10.1155/2017/2354253.
2. Brian J. Wentworth, Helmy M. Siragy. Adrenal Insufficiency in Cirrhosis. ournal of the Endocrine Society, 2022, 6, 1–11 https://doi.org/10.1210/jendso/bvac115
3. Marik PE, Gayowski T, Starzl TE, Group; HCRaAPS. The hepatoadrenal syndrome: a common yet unrecognized clinical condition. *Crit Care Med.* 2005;33(6):1254-1259. doi:10.1097/01.ccm.0000164541.12106.57
4. Bornstein SR, Allolio B, Arlt W, *et al.,* Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2016;101(2):364-389. doi:10.1210/jc.2015-1710
5. Lovato CM, Thévenot T, Borot S, *et al.,* Decreased maximal cortisol secretion rate in patients with cirrhosis: relation to disease severity. *JHEP Rep* 2021;3(3):100277. doi: 10.1016/j.jhepr.2021.100277 Wentworth BJ, Haug RM, Northup PG, Caldwell SH, Henry ZH.
6. Abnormal cholesterol metabolism underlies relative adrenal insufficiency in decompensated cirrhosis. *Liver Int.* 2021;41(8):1913-1921. doi:10.1111/liv.14970
7. Annane D, Pastores SM, Arlt W, *et al.,* Critical illness-related corticosteroid insufficiency (CIRCI): a narrative review from a Multispecialty Task Force of the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM). *Intensive Care Med.* 2017;43(12): 1781-1792.doi:10.1007/s00134-017-4914-x.
8. Gaeun Kim, Ji Hye Huh, Kyong Joo Lee, Moon Young Kim, Kwang Yong Shim, Soon Koo Baik; Relative Adrenal Insufficiency in Patients with

Cirrhosis: A Systematic Review and Meta-Analysis. Dig Dis Sci DOI 10.1007/s10620-017-4471-8
9. Arabi YM, Aljumah A, Dabbagh O, *et al.,* Low-dose hydrocortisone in patients with cirrhosis and septic shock: a randomized controlled trial. CMAJ. 2010; 182:1971–1977.
10. El Damarawy M, Hamed G, Heikal A, *et al.,* Meld score as a predictor for hepato adrenal syndrome. J Am Sci. 2012; 8:208–211.
11. Acevedo J, Fernandez J, Prado V, *et al.,* Relative adrenal insufficiency in decompensated cirrhosis: relationship to short-term risk of severe sepsis, hepatorenal syndrome, and death. Hepatology. 2013; 58:1757–1765
12. Galbois A, Rudler M, Massard J, *et al.,* Assessment of adrenal function in cirrhotic patients: salivary cortisol should be preferred. J Hepatol. 2010; 52:839–845.
13. Mohamed Badr Mohamed, Gamal Hamed2, Ayman Heikal, and Hisham Darwish. Prevalence of Adenocortical Insufficiency in Patients with Liver Cirrhosis, Liver Cirrhosis with Septic Shock and in Patients with Hepatorenal Syndrome. Journal of American Science, 2011;7(6)
14. Paul E. Marik. Adrenal-exhaustion syndrome in patients with liver disease. Intensive Care Med (2006) 32:275–280. DOI 10.1007/s00134-005-0005-5
15. Oster H, Challet E, Ott V, *et al.,* The functional and clinical significance of the 24-hour rhythm of circulating glucocorticoids. *EndocrRev.* 2017;38(1):3-45. doi:10.1210/er.2015-1080.
16. Montagnese S, Middleton B, Mani AR, Skene DJ, Morgan MY. On the origin and the consequences of circadian abnormalities in patients with cirrhosis. *Am J Gastroenterol.* 2010;105(8):1773-1781. doi:10.1038/ajg.2010.86.
17. Montagnese S, Middleton B, Mani AR, Skene DJ, Morgan MY. Changes in the 24-h plasma cortisol rhythm in patients with cirrhosis. *J Hepatol*. 2011;54(3):588-90; author reply 590; authorreply 90-1. 10.1016/j.jhep.2010.08.015
18. Stewart PM, Burra P, Shackleton CH, Sheppard MC, Elias E. 11beta-Hydroxysteroid dehydrogenase deficiency and glucocorticoid status in patients with alcoholic and non-alcoholic chronic liver disease. *J Clin Endocrinol Metab.* 1993;76(3):748-751. doi:10.1210/ jcem.76.3. 8445034..
19. Escher G, Nawrocki A, Staub T, *et al.,* Down-regulation of hepatic and renal 11 beta-hydroxysteroid dehydrogenase in rats with liver cirrhosis. *Gastroenterology* 1998;114(1):175-184. doi:10.1016/s0016-5085(98)70645-6
20. Miller JP. Dyslipoproteinaemia of liver disease. *Baillieres Clin Endocrinol Metab* 1990;4(4):807-832. doi:10.1016/s0950-351x(05)80080-1.
21. Fernández J, Escorsell A, Zabalza M, *et al.,* Adrenal insufficiency in patients with cirrhosis and septic shock: effect of treatment with hydrocortisone on survival. *Hepatology* 2006;44(5):1288-1295. doi:10.1002/hep.21352
22. Fede G, Spadaro L, Tomaselli T, *et al.,* Adrenocortical dysfunction in liver disease: a systematic review. *Hepatology* 2012;55(4):1282-1291. doi:10.1002/hep.25573.
23. Arafah BM. Hypothalamic pituitary adrenal function during critical illness: limitations of current assessment methods. *J Clin Endocrinol Metab.* 2006;91(10):3725-3745. doi:10.1210/jc.2006-0674.
24. Hamrahian AH, Oseni TS, Arafah BM. Measurements of serum free cortisol in critically ill patients. *N Engl J Med.* 2004;350(16):1629- 1638. doi:10.1056/NEJMoa020266.
25. Meyer EJ, Torpy DJ, Chernykh A, *et al.,* Pyrexia and acidosis act independently of neutrophil elastase reactive center loop cleavage to effect cortisol release from corticosteroid-binding globulin. *Protein Sci.* 2020;29(12):2495-2509. doi:10.1002/pro.3982.
26. Boonen E, Meersseman P, Vervenne H, *et al.,* Reduced nocturnal ACTH-driven cortisol secretion during critical illness. *Am J Physiol Endocrinol Metab.* 2014;306(8): E883-E892. doi:10.1152/ ajpendo.00009.2014
27. Dorin RI, Qiao ZG, Bouchonville M, Qualls CR, Schrader RM, Urban FK. Characterization of cortisol secretion rate in secondary adrenal insufficiency. *J Endocr Soc.* 2017;1(7):945-956. doi:10.1210/js.2017-00198
28. Fede G, Spadaro L, Tomaselli T, Privitera G, Scicali R, Vasianopoulou P, *et al.,* Comparison of total cortisol, free cortisol, and surrogate markers of free cortisol in diagnosis of adrenal insufficiency in patients with stable cirrhosis. *Clin Gastroenterol Hepatol*. 2014;12(3):504-12. e8; quiz e23.e8; quiz e23-4. doi: 10.1016/j.cgh.2013.08.028