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IPOTERMIA PERSISTENTE E DELIRIUM COME MANIFESTAZIONI RIVELATRICI DI INSUFFICIENZA SURRENALICA CENTRALE NELLA CIRROSI

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Riassunto

L'insufficienza surrenalica centrale è rara e difficile da diagnosticare nei pazienti cirrotici fragili, poiché i sintomi si sovrappongono a quelli delle infezioni e delle alterazioni metaboliche. Un uomo di 70 anni con cirrosi Child-Pugh C10 e carcinoma epatocellulare multicentrico (stadio BCLC D) si è presentato con ipotermia persistente (32 °C) e delirium ipoattivo progressivo nonostante una terapia antibiotica ad ampio spettro per una polmonite basale sinistra. I livelli di cortisolo erano bassi, con ACTH inappropriatamente basso; la TC cerebrale non mostrava anomalie. La somministrazione di prednisone a basso dosaggio (10 mg/die) ha portato a una rapida normalizzazione della temperatura e a un marcato miglioramento neurologico entro 36 ore. L'ipotermia refrattaria può rappresentare un indicatore clinico sottostimato di insufficienza surrenalica nella cirrosi. La risposta clinica ai glucocorticoidi può essere decisiva ai fini diagnostici.

Introduction

Central adrenal insufficiency (CAI) is characterized by inadequate cortisol secretion due to impaired hypothalamic–pituitary stimulation, with preserved mineralocorticoid function.
In cirrhotic patients, diagnosis is challenging because symptoms overlap with infection, hepatic encephalopathy, metabolic disturbances, and terminal oncological progression. Furthermore, total cortisol levels are difficult to interpret due to reduced binding proteins. Persistent hypothermia and hypoactive delirium unresponsive to treatment should raise suspicion of clinically relevant CAI.

Case presentation

A 70-year-old institutionalized man with advanced alcohol-related and NASH-associated cirrhosis (Child-Pugh C10, MELD-Na 12), multicentric hepatocellular carcinoma (BCLC stage D), type 2 diabetes mellitus (insulin-treated), untreated hypothyroidism, post-traumatic epilepsy with moderate major neurocognitive disorder (Glasgow Coma Scale, GCS, baseline 14), and severe sarcopenia was admitted for progressive asthenia. Functional dependence was high. Since 2023, each episode of urinary tract infection had been associated with hypothermia (33–34 °C), representing a recurring clinical pattern.
On admission, the patient was drowsy, confused, GCS fluctuating between 12 (prevalent) and 13. Blood pressure was 134/77mmHg, HR 58bpm, SatO2 93%, Core temperature was 32 °C. He was markedly asthenic and apparently malnourished. Initial laboratory tests showed anemia, leukopenia, thrombocytopenia, hypoalbuminemia (albumin 32 g/L), and mildly elevated C-reactive protein; electrolytes were within normal range. No urinary infection was documented.
Initial differential diagnoses included infection-related delirium, hepatic encephalopathy, endocrine dysfunction, and acute neurological events.

Clinical course and diagnostic reasoning

Profound hypothermia, more severe than in previous episodes and resistant to passive rewarming, was the most striking feature. Neurological status deteriorated during the first week, with rapid development of hypoactive delirium (GCS 6–11).
CRP increased significantly (112 mg/L), and clinical and radiological findings were consistent with left basal pneumonia. Broad-spectrum antimicrobial therapy with piperacillin/tazobactam and respiratory support were initiated. Despite antimicrobial treatment and resolution of inflammatory markers, hypothermia persisted around 32 °C and mental status failed to improve. This dissociation between inflammatory response and persistent neurovegetative dysfunction prompted reconsideration of non-infectious causes.
Brain CT excluded hemorrhage, ischemia, or mass lesions. Thyroid function showed subclinical hypothyroidism without features of myxedema coma. No hypoglycemia, severe hyperammonemia, or major electrolyte disturbances (although a transient episode of hypernatremia) were observed during hospitalization.

Given the refractory presentation, hypothalamic–pituitary–adrenal (HPA) axis dysfunction was investigated. Basal serum cortisol was markedly low (89 nmol/L), with inappropriately low ACTH (3 pmol/L). No clinical signs of primary adrenal failure were present.
Pituitary MRI was considered but deferred due to severe frailty, limited short-term prognosis, and unfavorable risk–benefit ratio.

Parameter	Reference ranges	Units	Initial	Minimum	Maximum	Final
Sodium	135–145	mmol/L	141	139	155	141
Potassium	3.5–5.0	mmol/L	4.4	3.1	4.4	4.1
Ammonia	16–60	µmol/L	79	39	85	43
Glucose	3.9–5.6	mmol/L	5	4.2	5.6	4.7
Calcium	2.1–2.6	mmol/L	2.44	2.05	2.44	2.27
Creatinine	62–115	µmol/L	72	53	134	73
Urea	2.5–7.1	mmol/L	5.4	1.6	13.1	4.7
Hemoglobin	13.5–17.5	g/dL	9.2	8	10.5	10.3
Leukocytes	4.0–11.0	G/L	3.3	2.1	7.6	3.2
Platelets	150–450	G/L	15	10	137	64
Albumin	35–50	g/L	32	27	36	29
C-Reactive Protein	<5	mg/L	13	2	112	2
Cortisol (7.00 AM)	138–690	nmol/L	-	89	-	-
ACTH (7.00 AM)	2.2–13.3	pmol/L	-	3	-	-
TSH	0.4–4.0	mUI/L	13.6	7.07	13.6	8.6
fT3	3.5–6.5	pmol/L	3.6	2.7	4.5	3.8
fT4	12–22	pmol/L	11	11	13	11
Body temperature	36.5–37.5	°C	32	32	36.5	36.5

Tab 1: Key vital and laboratory parameters are shown to illustrate the clinical picture. Note the hypocortisolemia and the inappropriately low ACTH level relative to cortisol concentration.

Treatment and outcome

Low-dose prednisone (10 mg/day) was initiated. Clinical response was rapid and marked: within 36 hours, core temperature normalized and mental status improved significantly (GCS 14), with stabilization of GCS at 14 and recovery of alertness. This temporal relationship strongly supported CAI as the determinant factor underlying the clinical collapse, beyond infectious or metabolic contributors.

Discussion

In cirrhotic patients, adrenal insufficiency is increasingly recognized, although prevalence estimates vary widely. In advanced cirrhosis, interpreting total serum cortisol is challenging: approximately 90% of circulating cortisol is bound to Corticosteroid-Binding Globulin (CBG) and albumin. Altered cortisol-binding proteins complicate interpretation of total cortisol values, making integration of biochemical data with clinical context essential. In patients with Child-Pugh C cirrhosis, hepatic synthesis of these proteins is severely impaired, leading to low total cortisol levels. However, in our patient, the diagnosis of CAI was confirmed not merely by low cortisol but by the inappropriately low ACTH during a state of severe clinical stress (hypothermia and pneumonia), which was highly suggestive of a failure of the central feedback mechanism.

In this patient, pneumonia plausibly explained inflammatory markers and contributed to delirium but could not account for persistent severe hypothermia and lack of neurological improvement despite adequate therapy. The overlapping pneumonia acted as a definitive stressor that exhausted the minimal adrenal reserve, leading to the thermal and neurological collapse observed. The recurring pattern of infection-associated hypothermia suggested underlying HPA axis state of maximum vulnerability, consistent with stress-related adrenal insufficiency in advanced stage cirrhosis (Child-Pugh C10, BCLC D).

A transient episode of hypernatremia (maximum 155 mmol/L) occurred during the second week and was promptly corrected with fluid adjustment without clinical improvement. Particularly, given its transient nature, temporal dissociation from neurological worsening, and rapid correction without clinical improvement, hypernatremia was considered unlikely to have contributed significantly to the neurological deterioration. Similarly, hepatic encephalopathy was excluded: although ammonia was mildly elevated at admission, it normalized with mild laxative therapy without any neurological or thermal improvement.

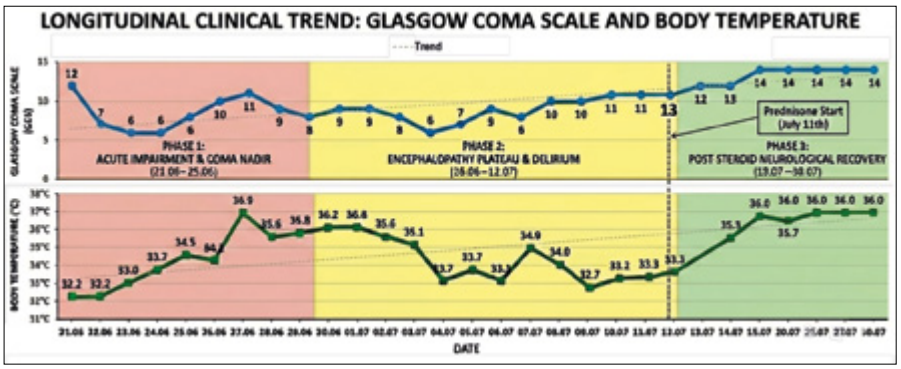

Fig 1: Timeline and comparison between GCS and temperature during hospitalization, with the corresponding overall trend for each parameter.

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This clinical-biochemical dissociation confirms that isolated hypernatremia and hyperammonemia were bystanders and not the cause of the collapse.

The relationship between infection and CAI in cirrhosis is bidirectional. While the patient may have a baseline HPA-axis vulnerability (stress-related adrenal insufficiency), an acute infection like pneumonia acts as a definitive stressor. In this fragile state, the axis fails to mount an adequate 'relative' cortisol response. The main pitfall in interpreting HPA function during stress in such patients is the overlap of symptoms with sepsis; however, the persistence of neurovegetative dysfunction (refractory hypothermia) despite the resolution of inflammatory markers (CRP) should be considered a red flag for adrenal exhaustion. Electrolyte findings were nonspecific, highlighting that absence of classic Addisonian features does not exclude clinically relevant CAI. Exclusion of acute neurological, metabolic, and infectious causes progressively narrowed the differential diagnosis.

Regarding treatment, Prednisone (10 mg/day) was preferred over hydrocortisone for two reasons: its higher glucocorticoid-to-mineralocorticoid potency ratio and its longer half-life. In a Child-Pugh C patient with pre-existing fluid overload and ascites, the mineralocorticoid activity of hydrocortisone would have carried a high risk of exacerbating sodium retention. Given the central nature of the deficit and the patient's severe frailty, we opted for a long-term low-dose replacement strategy to maintain clinical stability and prevent recurrent hypothermic crises.

The rapid normalization of temperature and consciousness following glucocorticoid replacement served as both therapeutic intervention and diagnostic confirmation.

Conclusion

Refractory hypothermia may represent an under-recognized clinical marker of adrenal insufficiency in cirrhosis. This case illustrates that central adrenal insufficiency may represent the unifying diagnosis in frail cirrhotic patients presenting with persistent hypothermia and hypoactive delirium refractory to standard treatment. In such contexts, reliance on laboratory values alone is insufficient. A structured diagnostic approach integrating clinical pattern recognition, exclusion of common precipitants, and therapeutic response to glucocorticoids is essential to avoid missing clinically relevant CAI.

Persistent Hypothermia and Delirium Revealing Central Adrenal Insufficiency in Cirrhosis

Abstract

Central adrenal insufficiency is uncommon and difficult to diagnose in frail cirrhotic patients, as symptoms overlap with infection and metabolic disturbances. A 70-year-old man with Child-Pugh C10 cirrhosis and multicentric hepatocellular carcinoma (BCLC stage D) presented with persistent hypothermia (32 °C) and progressive hypoactive delirium despite broad-spectrum antibiotic therapy for left basal pneumonia. Cortisol levels were low with inappropriately low ACTH; brain CT was unremarkable. Low-dose prednisone (10 mg/day) led to rapid normalization of temperature and marked neurological improvement within 36 hours. Refractory hypothermia may represent an under-recognized clinical marker of adrenal insufficiency in cirrhosis. Clinical response to glucocorticoids may be diagnostically decisive.

Keywords: central adrenal insufficiency, cirrhosis, hypothermia, delirium, glucocorticoids

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Declarations

- Authors' role in the preparation of the manuscript:
  P.M.: clinical management of the patient, data collection, literature review, manuscript drafting and critical revision,
  F.C.: endocrinology consultation, interpretation of clinical data and critical revision of the manuscript,
  A.C.: specialist consultation, interpretation of clinical data and critical revision of the manuscript,
  D.H.: clinical management, critical revision of the manuscript and specialist consultation
  All authors approved the final version of the manuscript.
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