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Case Report

Severe Hyponatremia Unveiling Isolated ACTH Deficiency in Chronic Alcohol Abuse: A Diagnostic Challenge

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Abstract: Isolated adrenocorticotropic hormone deficiency (IAD) secondary to chronic alcohol abuse is an extremely rare condition, often underdiagnosed due to nonspecific clinical features overlapping with complications of alcoholism. A 42-year-old Brazilian male with chronic alcohol abuse was admitted for hematemesis and severe hyponatremia refractory to conventional therapy. Biochemical evaluation revealed profound hypocortisolism with inappropriately low adrenocorticotropic hormone (ACTH) levels and normal pituitary function and imaging. A comprehensive workup ruled out other potential causes of hyponatremia. Diagnosis of IAD was hypothesized. Hydrocortisone replacement therapy led to rapid clinical improvement and normalization of sodium levels. This case highlights the importance of considering IAD in chronic alcoholics with unexplained hyponatremia. Early diagnosis and corticosteroid replacement therapy are essential to prevent life-threatening complications.

Keywords: Alcohol; Adrenocorticotropic hormone (ACTH); Sodium; Adrenal insufficiency.

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1. Introduction

Isolated adrenocorticotropic hormone (ACTH) deficiency (IAD) is a rare and often under-recognized cause of potentially life-threatening hyponatremia, especially in patients with chronic alcohol abuse. While Pseudo-Cushing syndrome is a well-recognized feature of chronic alcoholism [1], true suppression of the hypothalamic-pituitary-adrenal (HPA) axis secondary to alcohol abuse is extremely rare. To date, less than 10 cases have been described in the literature, mainly presenting severe hypoglycemic episodes and hyponatremia [3-8].

The detailed underlying pathophysiology remains unclear; however, alcohol-induced neuroendocrine dysregulation resulting in HPA axis inhibition has been implicated [1,9,10]. Because of overlapping symptoms and biochemical features with acute alcohol toxicity, this condition may be riskily overlooked and misdiagnosed [11]. This report presents a case of life-threatening hyponatremia during active esophageal variceal bleeding in a patient with chronic alcohol abuse, attributed to IAD, and includes a brief literature review of this rare association.

2. Case Report

In October 2023, a 42-year-old Brazilian male was admitted to the emergency department (ED), presenting with an episode of hematemesis and melena. His medical history was significant for a long-standing alcohol abuse, and he was not taking any medications; no other significant medical conditions were reported. Laboratory investigations revealed neutrophilic lymphocytosis (WBC 12000/ μL, Neu 75%), severe normocytic anemia (Hb

7.4 g/dL, Ht 27%, MCV 88 fL) and thrombocytopenia (80000/μL), which required blood transfusions, and impaired hepatic function (GOT 109 U/L, ALT 62 U/L, ALP 110 U/L, γGT 280 U/L, Total Bilirubin 2.3 mg/dl, INR 1.6). Electrolyte evaluation showed a profound hyponatremia (122 mmol/L [135-148]) with hypokalemia (3.14 mmol/L [3.5-5]) and hypoglycemia (55 mg/dL [60-100]). Serum osmolality was 274 mOsm/kg, urine osmolality 280 mOsm/kg, and urinary sodium concentration 85.8 nmol/l. Toxicological assessment was negative for cannabinoid, hypnotics, cocaine, or opiates exposure, while blood alcohol testing was positive.

Physical examination revealed general distress, confusion, and a hypotensive status with dehydration. No clinical signs of alcohol withdrawal syndrome (e.g., tremors, hallucinations) were observed during hospitalization. Hepatomegaly and mild ascites were also observed and confirmed by abdominal ultrasound scan (US). After appropriate hemodynamic support, evaluation with esophagogastroduodenoscopy (EGDS) was early performed and active bleeding varices were properly treated with ligation. Proton pump inhibitors (PPI), vitamin K, antibiotic therapy and prophylactic terlipressin to prevent recurrent varicose bleeding were instituted.

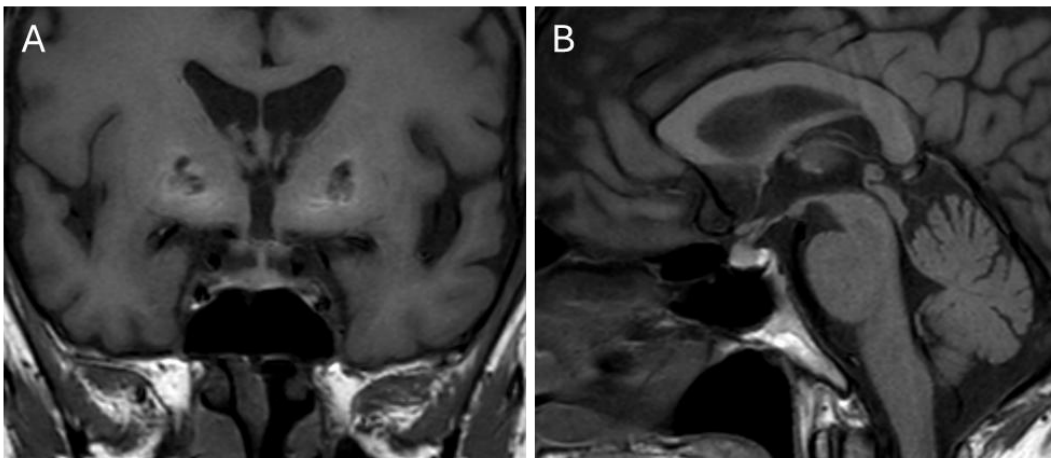
During the hospitalization, potassium and glucose were supplemented with benefit (4.16 mmol/L and 92 mg/dl, respectively), while sodium levels responded poorly both to fluid restriction (123 mmol/L) and hypertonic saline infusions (126 mmol/L). Renal disease and cardiac failure were excluded, as cardiac US showed a preserved biventricular function. A Total-body contrast enhanced Computed Tomography (TB-CT) scan was performed to exclude the presence of any neoplastic disorders known to potentially cause a syndrome of inappropriate antidiuretic hormone secretion (SIADH), and to exclude abnormalities of the adrenal glands, and no pathological findings were observed.

Further laboratory investigations revealed a marked reduction of 8 am cortisol concentrations (14 ng/ml, [48-195]) associated with an inappropriately low ACTH levels (4.2 pg/ml, [7.2-52]). Both aldosterone and plasma renin concentrations, along with pituitary hormonal function, were within normal ranges. Thyroid function tests showed a mild reduction in fT3 with normal TSH and fT4, suggestive of non-thyroidal illness síndrome (Table 1). Iatrogenic inhibition of the HPA axis was excluded since no corticosteroids were taken either previously or during hospitalization. In addition, a pituitary contrast enhanced magnetic resonance (MRI) was performed revealing normal morphology without stalk deviation, enlargement, or evidence of neoplastic or inflammatory lesions (Figure 1). A comprehensive rheumatologic-immunological evaluation was performed, ruling out autoimmune disorders. Based on these findings, a diagnosis of IAD secondary to chronic alcohol abuse was hypothesized.

Table 1. Endocrine laboratory profile.

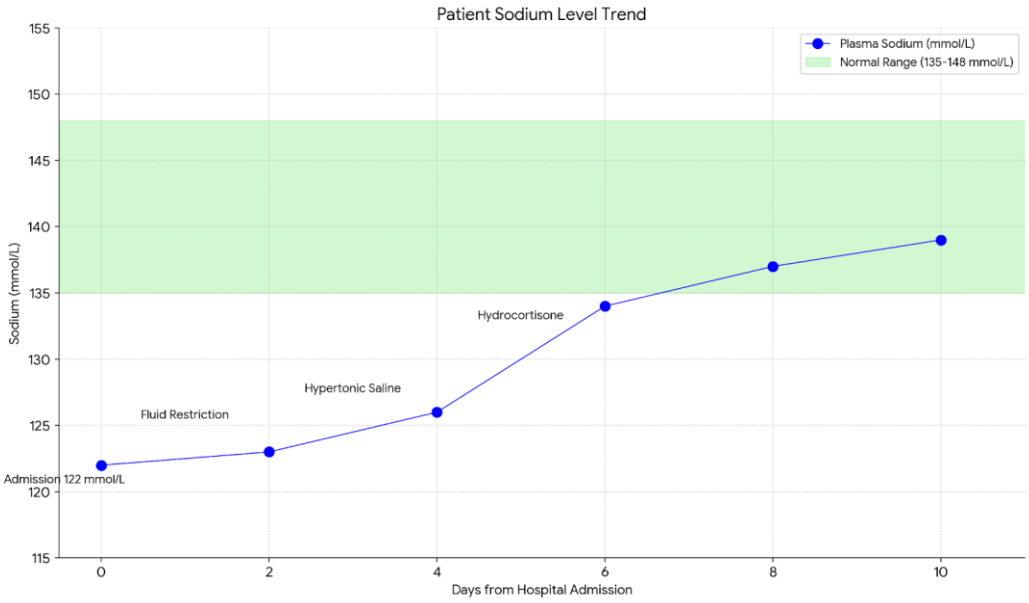
Analyte	Value	Reference range
ACTH, pg/ml	4.2	7.2 - 52
Cortisol, ng/ml	14	48 - 195
FSH, mIU/mL	6.8	1.5 - 12.4
LH, mIU/mL	4.3	1.8 - 8.6
Total Testosterone, ng/ml	3.76	2.49 - 8.36
IGF1, u/L	121	116 - 358
TSH, mU/L	0.97	0.4 - 5
fT4, ng/dl	1.24	0.9 - 1.7
fT3, pg/ml	1.93	2 - 4.4
Aldosterone, ng/dl	152	12 - 240
Renin, mU/L	34.7	2.8 - 39.9

Figure 1. T1-weighted coronal (left) and sagittal (right) pituitary MRI showing no abnormality in the hypothalamus, hypophyseal stalk, and pituitary gland.



Treatment with hydrocortisone replacement therapy 10mg twice daily was instituted, leading to rapid clinical and biochemical improvement. Patients' blood pressure was normalized, and sodium concentration gradually returned within normal values (134 - 139 mmol/L [135-148]). Once the hepatological parameters were also stable, the patient was discharged and advised to attend endocrinological and hepatological follow-up. The patient was followed up at 3 months, confirming persistent central adrenal insufficiency (ACTH 6 pg/ml [7.2-52], cortisol 21 ng/ml [48-195]. However, reliable data on sustained alcohol abstinence were not available, and he was subsequently lost to follow-up, preventing long-term evaluation of HPA axis recovery. Figure 2 shows sodium levels trend during hospitalization and Figure 3 summarizes the main chronological events and diagnostic-therapeutic flow-chart of the presented case.

Figure 2. Sodium levels trend during hospitalization.

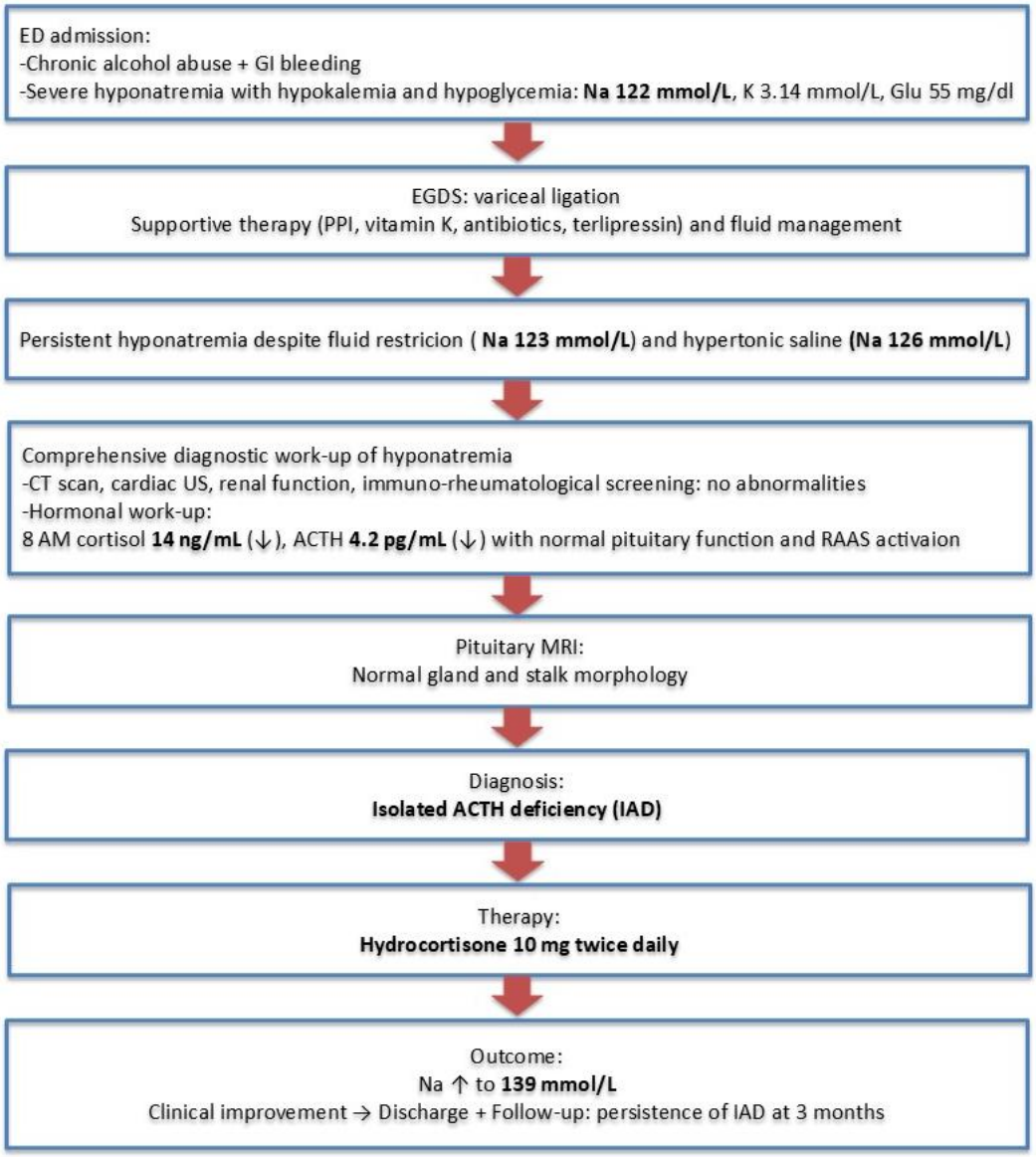


3. Discussion

IAD is a rare disorder characterized by low cortisol levels due to deficient ACTH secretion, in the presence of normal pituitary anatomy and preserved secretion of other

anterior pituitary hormones [12]. It may be congenital [13], or more commonly arising secondary to autoimmune hypophysitis, traumatic brain injury, immune checkpoint inhibitors, or paraneoplastic syndromes [14-16]. The clinical presentation is often vague—fatigue, anorexia, weight loss, abdominal pain and hypotension are frequent—but hyponatremia occurs in only ~20% of cases [17].

Figure 3. Main chronological events and diagnostic-therapeutic flow-chart of the presented case.



Legend: ED= emergency departement; GI=gastrointestinal; EGDS= esophagogastroduodenoscopy; PPI= proton pump inhibitors; Na= sodium; K= potassium; Glu=glycemia; CT= total body computed tomography; US= ultrasound scan; MRI= magnetic risonance; IAD= isolated ACTH deficiency.

In contrast, hyponatremia appears to be a predominant and consistent feature in the alcohol-associated cases. In our patients, laboratory abnormalities such as lymphocytosis, hypoglycemia, and isolated hyponatremia in the absence of hyperkalemia were strongly suggestive of central adrenal insufficiency. Dynamic stimulation testing (e.g., Cosyntropin test) remains the diagnostic gold standard. Although in this clinical setting the diagnosis was supposed by a combination of markedly low morning cortisol levels accompanied by inappropriately suppressed ACTH concentrations, the lack of a stimulation test

represents a limitation. However, in acute settings with compelling clinical and biochemical findings, dynamic testing may not always be feasible or necessary [12,18].

To date, fewer than 10 cases of alcohol-associated IAD have been published (Table 2), primarily from the United States [3,5,6], Japan [4,8], and Europe [7]. To the best of the author's knowledge, this may represent the first case reported in Italy and the first involving a South American patient, although regional publications not indexed in major databases cannot be excluded. The initial description of this association dates to 1965, when Woeber and Arky reported a patient with recurrent alcohol-induced hypoglycemia due to IAD [3]. Since then, similar cases have been described, typically involving male patients presenting with hypoglycemia or hyponatremia responsive to corticosteroid replacement [4–8].

Although hyponatremia is a frequent finding in alcohol-related liver disease, its occurrence is typically accompanied by activation of the renin–angiotensin–aldosterone system (RAAS) [19]. In this case, normality of plasma renin and aldosterone levels despite hypotension and hyponatremia, along with the refractoriness to conventional treatment and the rapid normalization of sodium levels following corticosteroid replacement, strongly suggested a central adrenal insufficiency. Only one fatality has been reported among known cases of alcohol-related IAD, in a patient who died of progressive hepatorenal syndrome despite hormone replacement therapy [6]. These findings highlight the importance of promptly recognizing hypocortisolism in alcohol abusers presenting with refractory hyponatremia.

Table 2. Summary of Reported Cases of Alcohol-Associated Isolated ACTH Deficiency (including the present case).

Reference	Number of patients	Sex	Age	Country	Clinical presentation	Main laboratory abnormality	Treatment	Outcome
[3]	1	M	54	USA	Hypoglycemic coma	Hypoglycemia	Oral Hydrocortisone	Clinical and biochemical recover
[5]	1	M	43	USA	Hypoglycemic episode	Hypoglycemia	Oral Hydrocortisone	Clinical and biochemical recover
[4]	1	M	48	Japan	Hypoglycemic coma	Hypoglycemia	Oral Hydrocortisone	Clinical and biochemical recover
[6]	3	M	54	USA	Confusional state and decompensated liver disease	Hyponatremia	Oral Hydrocortisone	Clinical and biochemical recover
		F	49		Sepsis and decompensated hepatic failure	Hyponatremia	Oral Hydrocortisone	Death
		M	40		Collapse and grand mal seizures	Hyponatremia	Oral Hydrocortisone	Clinical and biochemical recover

[7]	2	M	65	Poland	Hypotonia	Hyponatremia	Oral Hydrocortisone	Clinical and biochemical recover
		M	68		Weight loss	Hyponatremia	Oral Hydrocortisone	Clinical and biochemical recover
[8]	1	M	81	Japan	Hypoglycemic coma	Hypoglycemia	Oral Hydrocortisone	Clinical and biochemical recover
Present case	1	M	42	Italy	Variceal bleeding	Hyponatremia	Oral Hydrocortisone	Clinical and biochemical recover

While alcoholic hypoglycemia is a well-recognized clinal entity related to the impairment of hepatic gluconeogenesis, the physiopathology of ethanol-associated IAD remains incompletely understood. Alcohol modulation of the HPA axis has been comprehensively investigated in both animal and human models during the last decades, with heterogeneous results, depending on multiple factors such doses and duration of exposure. Acute alcohol administration transiently stimulates ACTH and cortisol secretion in a dose related fashion [20], but chronic ethanol exposure suppresses the HPA axis [1,9,10]. Consistently, alcohol addiction leads to a dampened neuroendocrine state, disrupting not only ACTH secretion but also other pituitary axis. Although animal studies suggest neuroendocrine-mediated effects of alcohol on hypothalamic-pituitary function, these mechanisms remain speculative in humans.

Proposed mechanisms include impaired hypothalamic-pituitary signaling and responsiveness to secretagogues due to alcohol-induced neurotransmitter imbalances and intra-cerebral amines depletion [21,22]: increased GABAergic and dopaminergic tone, enhanced endogenous opioid activity, and atrial natriuretic peptide (ANP) release, all of which inhibit corticotropin-releasing hormone (CRH) and ACTH synthesis and secretion [23,24]. Moreover, alcohol inhibits glutamatergic signaling via NMDA receptor antagonism, further blunting ACTH response [25]. Hypocortisolism may in turn fail to suppress vasopressin (AVP) release, contributing to euvolemic hyponatremia [26]. Human studies have demonstrated blunted ACTH and cortisol responses to CRH stimulation [27], while administration of naltrexone has been shown to increase both ACTH and cortisol levels in chronic alcoholics, supporting endogenous opioid-mediated suppression of the HPA axis [28]. Moreover, cerebrospinal fluid (CSF) analyses have revealed altered CRH concentrations in individuals with alcohol dependence [27]. In summary, although experimental evidence in the experiment suggests that chronic alcohol abuse can suppress the HPA axis in humans, the evidence remains limited and largely indirect—particularly in cases of IAD.

In conclusion, although rare, IAD should be considered in the differential diagnosis of chronic alcohol abusers presenting severe or refractory hyponatremia. Early recognition and corticosteroid replacement can be lifesaving in these patients.

4. Conclusion

IAD due to chronic alcohol abuse is a rare cause of hyponatremia. Clinical features are non-specific and may overlap with those of chronic alcohol intoxication and decompensated liver disease. Therefore, diagnosis is subtle and frequently delayed, but it is of paramount importance since precipitating factors can lead to life-threatening adrenal crisis. Assessment of morning cortisol and ACTH values and, when indicated, dynamic stimulation testing are recommended in all patients with chronic alcohol abuse presenting with unexplained and refractory hyponatremia (having excluded most common forms,

iatrogenic and SIADH), hypoglycemia or persistent hemodynamic instability. Corticosteroid replacement therapy usually induces a rapid resolution of clinical manifestations and laboratory abnormalities.

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Conflicts of Interest: None.

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