Section: General Medicine

Case Report

UNMASKING AGITATION BEYOND THE USUAL SUSPECTS: SECONDARY ADRENAL INSUFFICIENCY PRESENTING AS HYPERACTIVE DELIRIUM

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Received *: 05/04/2026*
Received in revised form *: 25/05/2026*
Accepted *: 10/06/2026*

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DOI: 10.70034/ijmedph.2026.2.602

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2026; 16 (2); 3658-3662

ABSTRACT

Background: Delirium in elderly patients is commonly attributed to metabolic, infectious, or neurological causes, while endocrine etiologies are often overlooked. Secondary adrenal insufficiency is an uncommon but reversible cause that may occasionally present with neuropsychiatric symptoms.

Case Presentation: An 80-year-old male with multiple comorbidities presented with upper gastrointestinal bleeding and was managed in the intensive care unit. During hospitalization, he developed persistent hyperactive delirium characterized by agitation, sleep disturbance, and altered sensorium. Initial evaluation, including neuroimaging and metabolic correction, did not explain the ongoing symptoms. Further workup revealed hyponatremia, low free T3 levels, and a history of recent parenteral therapy suggestive of exogenous steroid exposure. Hormonal evaluation showed low morning cortisol with inappropriately normal adrenocorticotropic hormone levels, consistent with secondary adrenal insufficiency.

Intervention and Outcome: The patient was initiated on corticosteroid replacement therapy, resulting in rapid and marked improvement in neuropsychiatric symptoms.

Conclusion: Secondary adrenal insufficiency should be considered in cases of persistent or atypical delirium, particularly in elderly patients with a history of steroid exposure and unexplained hyponatremia. Early recognition and treatment can lead to dramatic clinical recovery and prevent unnecessary interventions.

Keywords: Delirium, Secondary adrenal insufficiency, Hyponatremia, Steroid-induced adrenal suppression, Elderly, Neuropsychiatric symptoms.

INTRODUCTION

Delirium is a common and serious neuropsychiatric syndrome in elderly patients, particularly in acute care and intensive care settings.[1-3] It is characterized by an acute disturbance in attention, awareness, and cognition, often with a fluctuating course.[1,2] The etiology of delirium is typically multifactorial, with common causes including infections, metabolic disturbances, medications, and structural neurological abnormalities.[2,3] Despite extensive evaluation, a subset of patients continues to have unexplained or persistent symptoms, warranting consideration of less common causes.[3]

Adrenal insufficiency is an underrecognized but important reversible cause of delirium.[4-7] Secondary adrenal insufficiency, most commonly resulting from suppression of the hypothalamic–pituitary–adrenal (HPA) axis due to exogenous glucocorticoid use, can present with nonspecific symptoms such as fatigue, hyponatremia, and neuropsychiatric manifestations.[4,6,8] These manifestations may include depression, cognitive impairment, psychosis, and delirium, often leading to misdiagnosis as primary psychiatric or neurological disorders.[11,12]

Hyponatremia, a frequent finding in adrenal insufficiency, further contributes to altered mental status through cerebral edema and neuronal dysfunction.[8,14] Additionally, glucocorticoid deficiency affects multiple neurochemical pathways and brain regions, including the hippocampus and

prefrontal cortex, thereby exacerbating cognitive and behavioural disturbances.[6,13]

We report a case of an elderly male with persistent hyperactive delirium initially attributed to ICU-related causes, who was subsequently diagnosed with secondary adrenal insufficiency due to exogenous steroid exposure. This case highlights the importance of thorough history-taking and the need to consider endocrine etiologies in atypical or treatment-resistant delirium.

CASE PRESENTATION

Patient Information: An 80-year-old male presented with complaints of generalized tiredness for five days, followed by an episode of hematemesis and melena on the day of admission. He was previously independent in activities of daily living and functionally active prior to the current illness.

Past Medical History

- Peptic ulcer disease with a history of perforation, status post gastrojejunostomy several years prior
- Past history of ischemic stroke, on antiplatelet therapy and statin
- Benign prostatic hyperplasia, on tamsulosin
- Prediabetes

Personal and Social History

- History of tobacco chewing
- Occasional alcohol consumption
- No known history of recent infections or trauma

Initial Hospital Course: The patient was hemodynamically stabilized in the emergency department with appropriate resuscitative measures. In view of ongoing upper gastrointestinal bleeding and the lack of gastroenterology services, he was referred to a higher center and admitted to the intensive care unit under specialist care.

Baseline laboratory investigations, including complete blood count, renal and liver function tests, inflammatory markers, and coagulation profile, were within normal limits except for mild anemia. Upper gastrointestinal endoscopy revealed an ulcer at the gastrojejunostomy site, and a rapid urease test was positive for Helicobacter pylori. Serum electrolyte analysis demonstrated hyponatremia, while potassium levels remained within normal range.

The patient was managed conservatively with intravenous fluids, proton pump inhibitors, and correction of electrolyte imbalance. He remained clinically stable during the initial course of hospitalization.

However, on the third day of ICU admission, he developed acute onset neuropsychiatric symptoms, including agitation, altered sensorium, decreased sleep, and irrelevant speech, consistent with hyperactive delirium. Neuroimaging showed only chronic infarcts, and metabolic abnormalities, including hyponatremia, were corrected. Neurology and psychiatry consultations were obtained, and a provisional diagnosis of ICU-related delirium was made. He was managed symptomatically and subsequently discharged after clinical stabilization.

Development of Delirium: On the third day of ICU admission, the patient developed acute neuropsychiatric symptoms, including agitation, altered sensorium, decreased sleep, irrelevant speech, and wandering behaviour, consistent with hyperactive delirium.

Neuroimaging showed only chronic infarcts. Hyponatremia was corrected, and no acute neurological or infectious cause was identified. He was diagnosed with ICU-related delirium and managed symptomatically following neurology and psychiatry consultations.

Persistence of Symptoms: Despite initial management and discharge with a provisional diagnosis of ICU-related delirium, the patient continued to exhibit persistent neuropsychiatric symptoms. These included ongoing agitation, sleep disturbances, intermittent confusion, and behavioural abnormalities, which were disproportionate to his clinical recovery from the upper gastrointestinal bleeding episode.

Given the persistence and atypical course of symptoms despite correction of metabolic abnormalities and absence of new neurological findings, the patient was readmitted for further evaluation. The lack of sustained improvement with standard delirium management raised suspicion for an underlying organic etiology beyond ICU-related causes.

This prompted a comprehensive reassessment, including a detailed review of medications, repeat laboratory investigations, and re-evaluation of clinical history, ultimately leading to the identification of an endocrine cause for the patient's persistent symptoms.

Diagnostic Assessment: In view of persistent and unexplained delirium, a comprehensive diagnostic reassessment was undertaken.

Clinical Evaluation: A detailed clinical review revealed ongoing features of hyperactive delirium, including agitation, sleep disturbance, and fluctuating cognition. Additionally, there was a suggestion of proximal muscle fatigue, though no objective focal neurological deficits were identified.

Medication Review: A thorough review of medications was performed to identify potential drug-induced causes. The patient had been receiving:

- H. pylori eradication therapy
- Atorvastatin
- Tamsulosin
- Tolvaptan
- Sertraline
- Lorazepam

Although some of these medications can contribute to altered mental status, there was no clear temporal correlation or sufficient evidence to fully explain the persistence of symptoms.

Laboratory Investigations

Repeat laboratory evaluation showed:

- Mild anemia

- Hyponatremia (previously corrected but etiologically unexplained)
- Low free triiodothyronine (FT3) with normal FT4 and thyroid-stimulating hormone
- Vitamin D deficiency

The isolated low FT3 level with otherwise normal thyroid function tests was consistent with non-thyroidal illness syndrome in the setting of systemic illness.

Neuroimaging: Computed tomography of the brain demonstrated chronic infarcts consistent with the patient's prior history of stroke, with no evidence of acute pathology to account for the current presentation.

Critical Historical Clue: A detailed re-evaluation of history revealed that the patient had received a course of intravenous injections for ocular symptoms approximately one month prior to presentation. These were presumed to contain corticosteroids, raising the possibility of hypothalamic–pituitary–adrenal (HPA) axis suppression.

Endocrine Evaluation

Hormonal investigations were performed to assess adrenal function:

- 8 a.m. serum cortisol: Low
- Adrenocorticotropic hormone (ACTH): Inappropriately normal

A cosyntropin stimulation test could not be performed because of non-availability of reagents and the need for urgent therapeutic decision-making in a clinically unstable patient.

Final Diagnosis

Based on the combination of:

- Low morning cortisol levels
- Inappropriately normal ACTH
- History of recent exogenous steroid exposure
- Absence of structural adrenal abnormalities a diagnosis of secondary adrenal insufficiency due to exogenous glucocorticoid use was established.

Table 1: Timeline of Clinical Events

Time Course	Clinical Events
Day 0	Presentation with hematemesis, melena, and generalized tiredness
Day 1	ICU admission, stabilization, baseline investigations; hyponatremia identified and correction initiated
Day 1–2	Endoscopy: gastrojejunostomy ulcer, RUT positive
Day 3	Onset of delirium (agitation, altered sensorium, sleep disturbance)
Day 3–5	Neuroimaging: old infarcts; treated as ICU delirium
Discharge	Persistent neuropsychiatric symptoms
Readmission	Further evaluation for persistent delirium
Later	History of steroid exposure identified
Evaluation	Low cortisol, normal ACTH → secondary adrenal insufficiency
Treatment	Steroid replacement initiated
Outcome	Rapid improvement in symptoms

Notes: Day 0 denotes initial presentation. ICU: Intensive Care Unit; RUT: Rapid urease test. Delirium developed on day 3 of ICU stay and persisted despite correction of metabolic abnormalities. Subsequent identification of prior steroid exposure and hormonal evaluation confirmed secondary adrenal insufficiency, with marked improvement following corticosteroid therapy.

Table 2: Laboratory Findings

Investigation	Result	Interpretation
Hemoglobin	Mild anemia	Secondary to upper gastrointestinal bleeding
Serum Sodium	Low	Hyponatremia
Serum Potassium	Normal	—
FT3	Low	Impaired T4 to T3 conversion
FT4	Normal	—
TSH	Normal	—
8 AM Cortisol	Low	Adrenal insufficiency
ACTH	Inappropriately normal	Secondary adrenal insufficiency
Vitamin D	Low	Deficiency

Notes: Laboratory findings revealed hyponatremia with preserved potassium levels, helping differentiate secondary from primary adrenal insufficiency. Low cortisol with inappropriately normal ACTH confirmed the diagnosis, while low FT3 reflected impaired peripheral thyroid hormone conversion.

Table 3: Differential Diagnosis of Delirium

Diagnosis	Supporting Features	Reason for Exclusion
ICU-related delirium	ICU stay, acute onset	Symptoms persisted despite symptomatic treatment and after discharge
Hyponatremia-related metabolic encephalopathy	Low serum sodium	No improvement after correction
Stroke (new event)	Past history of stroke	No acute findings on imaging
Drug-induced delirium	Multiple medications	No clear temporal association
Infection	Common cause in elderly	No fever or leukocytosis
Adrenal insufficiency	Hyponatremia, fatigue, steroid exposure, low serum cortisol	Confirmed diagnosis

Notes: Common causes of delirium were systematically excluded. Persistence of symptoms despite correction of metabolic factors and absence of structural or infectious etiology prompted evaluation for endocrine causes, leading to the diagnosis of secondary adrenal insufficiency.

Table 4: Key Clinical Clues Suggesting Adrenal Insufficiency

Clinical Feature	Significance
Persistent delirium	Not explained by common causes
Hyponatremia	Common in cortisol deficiency
Normal potassium	Helps differentiate secondary from primary adrenal insufficiency
Low FT3	Impaired T4 to T3 conversion
History of steroid exposure	Key etiological clue
Rapid response to steroids	Diagnostic confirmation

Notes: The combination of persistent neuropsychiatric symptoms, hyponatremia with normal potassium, and a history of steroid exposure raised suspicion for secondary adrenal insufficiency. Rapid clinical improvement following corticosteroid therapy supported the diagnosis.

Therapeutic Intervention: Based on the diagnosis of secondary adrenal insufficiency, the patient was initiated on corticosteroid replacement therapy. Physiological doses of glucocorticoids were administered, with careful monitoring of clinical response and electrolyte status.

Supportive care, including correction of nutritional deficiencies and optimization of existing medications, was continued. No additional antipsychotic escalation was required following initiation of steroid therapy.

Outcome and Follow-Up: Following initiation of corticosteroid replacement therapy, the patient showed rapid and significant clinical improvement. Neuropsychiatric symptoms, including agitation, altered sensorium, and sleep disturbances, resolved progressively over a short period. The patient regained baseline cognitive function and returned to his previous level of daily activity.

Serum sodium levels normalized, and overall clinical status remained stable. No further episodes of delirium were observed during the hospital stay.

At follow-up, the patient remained asymptomatic with good functional recovery. He was continued on maintenance corticosteroid therapy with appropriate counseling regarding adherence and the need for stress-dose steroids during intercurrent illnesses.

DISCUSSION

This case highlights an uncommon but clinically significant cause of persistent delirium—secondary adrenal insufficiency due to exogenous steroid exposure. Delirium in elderly patients is often multifactorial and commonly attributed to infections, metabolic disturbances, medications, or neurological conditions.[1–3] However, when symptoms persist despite correction of these factors, less common etiologies such as endocrine disorders must be considered.[3,4]

Secondary adrenal insufficiency results from suppression of the hypothalamic–pituitary–adrenal (HPA) axis, most frequently due to exogenous glucocorticoid use.[4–6] The clinical presentation is often nonspecific and may include fatigue, anorexia, hyponatremia, and neuropsychiatric manifestations.[4,7] In this case, the patient presented predominantly with hyperactive delirium, which initially led to a provisional diagnosis of ICU-related delirium, delaying definitive diagnosis.

Neuropsychiatric symptoms in adrenal insufficiency are well documented and can range from mild cognitive impairment and depression to agitation, psychosis, and delirium.[11,12] The underlying mechanisms are multifactorial. Glucocorticoid deficiency affects hippocampal and prefrontal cortical function, leading to impaired cognition and behaviour.[6,13] Additionally, alterations in neurotransmitter systems and increased proopiomelanocortin-derived peptides, including endorphins, may contribute to hallucinations and psychotic features.[6]

Hyponatremia is a key biochemical abnormality in adrenal insufficiency and was present in this patient. It occurs due to increased antidiuretic hormone secretion and impaired free water clearance in the setting of cortisol deficiency.[8,14] Importantly, in secondary adrenal insufficiency, mineralocorticoid function is preserved, explaining the absence of hyperkalaemia, which can help differentiate it from primary adrenal insufficiency.[5,6]

Another notable finding in this case was low free triiodothyronine (FT3) levels with normal TSH and FT4, likely reflecting non-thyroidal illness syndrome (euthyroid sick syndrome), which is commonly observed in critically ill patients.[10] This pattern may further complicate endocrine interpretation during acute illness.

The diagnosis of secondary adrenal insufficiency in this case was ultimately established through careful history-taking, which revealed prior exposure to parenteral steroids. The finding of low morning cortisol with inappropriately normal ACTH levels supported the diagnosis.[4,7] Imaging of the adrenal glands was normal, consistent with a central etiology.

A key learning point from this case is the importance of revisiting the clinical history when patients fail to respond to standard treatment. The persistence of delirium despite correction of metabolic abnormalities and absence of structural brain pathology should prompt consideration of endocrine causes.[3,4] Early recognition is crucial, as adrenal insufficiency is a potentially life-threatening but readily treatable condition.[4,7]

The rapid clinical improvement following corticosteroid replacement in this patient further supports the diagnosis and underscores the reversibility of symptoms when appropriately managed.[4,15] This case emphasizes that adrenal insufficiency can closely mimic primary psychiatric

disorders and should be included in the differential diagnosis of unexplained or treatment-resistant delirium, particularly in elderly patients.

CONCLUSION

Secondary adrenal insufficiency is an important and reversible cause of persistent delirium, particularly in elderly patients. This case underscores the need to consider endocrine etiologies when delirium is atypical, prolonged, or unresponsive to standard management. Careful history-taking, especially regarding prior steroid exposure, along with targeted hormonal evaluation, is essential for timely diagnosis. Early recognition and appropriate corticosteroid therapy can lead to rapid clinical recovery and prevent unnecessary interventions.

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