CASE REPORT

Case report: Primary empty Sella causing secondary adrenal insufficiency and severe yet asymptomatic hyponatremia

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Abstract
A 61-year-old man presented with incidental hyponatraemia to 118 mmol/L, to which he was asymptomatic. Diagnostic workup revealed a partially empty sella turcica on magnetic resonance imaging. He had associated secondary adrenal insufficiency but other hormonal axes were relatively unaffected. Treatment with cortisol replacement promptly resolved the hyponatraemia.

KEYWORDS
adrenal insufficiency, empty Sella, endocrinology, hyponatremia

1 | CASE DESCRIPTION

A 61-year-old gentleman presented to a regional hospital with a 48-h history of right painful calf swelling, preceded by a gradual onset of bilateral lower limb edema over 6 months. His past history included bilateral lower limbs varicose veins and previous right leg cellulitis and did not take regular medications. On examination, he had normal observations, an erythematous, bilateral pitting leg edema, a tender right calf, and the rest of the examination was otherwise unremarkable.

His admission blood tests were normal except for new incidental hyponatremia with a serum sodium of 118 mmol/L and a mildly raised C-reactive protein of 38 mg/L. Doppler ultrasound of his right leg revealed two sites of superficial venous thrombosis in the calf without evidence of deep venous thrombosis. On further questioning, he denied lightheadedness, falls, nausea, vomiting, or other symptoms of hyponatremia. Serum and urine osmolality and a spot urinary sodium were requested. The hyponatremia was managed initially by fluid restriction and furosemide 40 mg twice daily given the bilateral pedal edema and presumed hypervolemic hyponatremia. He was treated for right leg cellulitis with intravenous clindamycin 450 mg three times daily for 5 days and planned for a 6-week course of intermediate dose enoxaparin 60 mg twice daily to treat superficial venous thrombosis.

After 2 days of diuresis, his serum sodium level remained between 117–119 mmol/L. A transthoracic echocardiogram showed normal ejection fraction and heart valves. Contrast abdominal CT was performed to exclude malignancy given venous thrombosis and hyponatremia, which demonstrated only slightly enlarged bilateral inguinal nodes, likely a benign finding related to the bilateral edema. Serum osmolality was low at 248 mmol/kg with inappropriately elevated urinary sodium 87 mmol/L and osmolality 499 mOsm/kg suggesting syndrome of inappropriate antidiuretic hormone. His hyponatremia was further investigated with a morning cortisol, which returned low at <28 nmol/L, and maximum stimulated serum cortisol to short Synacthen test was also low at 122 nmol/L at 60 min. Adrenocorticotropic hormone was inappropriately normal at 42.2 ng/L, indicating secondary adrenal insufficiency. Pituitary MRI revealed a partially empty sella turcica.
sella turcica. Full endocrine hormonal workup (Table 1) revealed low dehydroepiandrosterone sulfate (DHEA-S) in keeping with corticotropin deficiency, as well as mild growth hormone deficiency.

He was commenced on oral cortisone 25 mg three times daily for 1 week, to transition to a maintenance dose of 25 mg in the morning and 12.5 mg in the evening. His serum sodium level increased to 133 mmol/L over three to 4 days before discharge.

This patient presented with right leg pain and swelling secondary to superficial venous thrombosis and subacute onset of bilateral pitting edema, complicated by an incidental finding of primary empty sella syndrome causing secondary adrenal insufficiency and severe yet asymptomatic hyponatremia.

2 | DISCUSSION

Hyponatremia is commonly encountered in practice and can have serious consequences without appropriate recognition and treatment. A broad diagnostic workup should always be considered to avoid missing important underlying diagnoses. Adrenal insufficiency is a rare but well-recognized cause of hyponatremia, which responds promptly to treatment and conversely can have catastrophic outcomes if missed.

Adrenal insufficiency often causes diagnostic confusion due to its highly variable, often very nonspecific presentation. Adrenal insufficiency is defined by a low serum cortisol, with 8 AM levels less than 100 nmol/L highly suggestive of the diagnosis. Cortisol is a physiologic inhibitor of antidiuretic hormone (ADH) secretion; and therefore, adrenal insufficiency can increase ADH secretion typically leading to syndrome of inappropriate ADH (SIADH) and euvolemic hyponatremia. Hyponatremia is more common in primary rather than secondary adrenal insufficiency, due to the additional effects of hypoaldosteronism on serum sodium.

Empty sella is characterized by the herniation of the subarachnoid space within the sella turcica, causing flattening of the pituitary gland and either partial or complete absence of pituitary tissue on MRI, which can result in endocrine dysregulation. Exact prevalence of empty sella is unclear with estimates of 8–35% based on autopsy and neuroimaging studies. Empty sella can be classified as primary or secondary, the latter being used to describe cases where antecedent causes such as tumor, infection, autoimmune disease, surgery, or radiation injury can be identified. Proposed etiologies of primary empty sella (PES), where no clear cause is identified, include congenital incomplete sella diaphragm formation and an increase in intracranial pressure causing herniation of subarachnoid fluid into the sella. Diagnosis is radiological with magnetic resonance imaging (MRI) being the modality of choice. Commonly PES is asymptomatic or can be associated with symptoms such as visual disturbance and headache particularly if intracranial pressure is raised, or symptoms attributed to hypopituitarism. Hypopituitarism is present in PES in approximately 52% (38 to 65%) of cases, with somatotropic deficiencies being most common, followed by gonadotropic insufficiency. Corticotropic and thyrotropic insufficiencies are rarer and appear to be more common when there is a complete empty sella.

The exact prevalence of hyponatremia due to empty sella and consequent secondary adrenal insufficiency is not known. Diederich et al. (2003) reviewed the causes of hyponatremia in 185 patients over a 20-year period, where 28 (15%) had secondary adrenal insufficiency as the main cause for hyponatremia, and 12 of these (6%) had empty sella. This study was selective for patients with complex or refractory hyponatremia requiring specialist endocrinology input, therefore the true prevalence of hyponatremia due to empty sella is probably lower than 6%, but perhaps more common than generally thought.

| Biochemical                        | Value | Reference range |
|------------------------------------|-------|-----------------|
| Serum sodium                       | 118a  | 135–145 mmol/L  |
| Serum osmolality                   | 248a  | 280–300 mmol/kg |
| Urine sodium                       | 87    | 20–150 mmol/L   |
| Urine osmolality                   | 499   | 40–1400 mmol/kg |
| Prolactin                          | 379   | 74–410 mIU/L    |
| ACTH                               | 42.2  | 7.2–63.3 ng/L   |
| Cortisol                           | <28a  | 100–535 nmol/L  |
| Synacthen stimulation              |       |                 |
| 30-min cortisol                    | 94a   | >450 nmol/L     |
| 60-min cortisol                    | 122a  | >500 nmol/L     |
| DHEA-S                             | 0.6a  | 1.3–9.8 mol/L   |
| TSH                                | 1.62  | 0.4–4.0 mIU/L   |
| fT4                                | 12.4  | 9.0–19.0 mIU/L  |
| GH                                 | 0.1   | <3.0 μg/L       |
| IGF1                               | 51a   | 55–186 μg/L     |
| LH                                 | 3.0   | 1.0–12.0 IU/L   |
| FSH                                | 3.0   | 0.6–12.1 IU/L   |
| Testosterone                       | 18.6  | 8.0–30.0 nmol/L |

Abbreviations: ACTH, Adrenocorticotropic hormone; DHEA-S, dehydroepiandrosterone sulfate; FSH, follicle-stimulating hormone; GH, growth hormone; IGF1, insulin-like growth factor 1; LH, luteinizing hormone; TSH, thyroid stimulating hormone. a indicates abnormal results.
In our patient, the presentation with painful leg swelling was unrelated to the hyponatremia, but importantly the leg edema was a distractor prompting initial treatment of hypervolemia hyponatremia with diuresis. The lack of improvement with diuresis prompted further investigation and underpins the importance of using a methodical approach in evaluating hyponatremia to find uncommon yet easily reversible underlying causes. Adrenal insufficiency is more often found in complete than partial empty sella, yet our patient with partial empty sella had hypocortisolism that was substantial enough to cause severe hyponatremia, which may have resulted in life-threatening complications if left undetected. Overall, while lower limb edema, hyponatremia, adrenal insufficiency, and even empty sella are not particularly rare presentations in isolation, seeing these entities in a single patient contemporaneously presented unique insights regarding the rarer etiologies of hyponatremia which lack obvious clinical clues and require an astute approach to diagnose.

The management approach for empty sella depends on its associated clinical manifestations. For an asymptomatic incidental finding of empty sella, the current recommendation would be to exclude secondary causes and perform pituitary hormonal diagnostic tests. The presence of neurologic manifestations may warrant neurosurgical referral particularly if intracranial pressure is raised. The primary treatment goal in our patient was to correct hyponatremia by cortisol replacement. Twice or thrice daily cortisone is preferred over longer-acting steroids such as prednisolone and dexamethasone as it most closely mimics physiologic cortisol release. A supraphysiologic dose of 25 mg three times daily was used initially which successfully treated the severe hyponatremia, with a view to transition to physiological maintenance doses of 25 mg in the morning and 12.5 mg in the evening. Importantly, sick day education was provided as patients with adrenal insufficiency require increased cortisone doses when unwell due to the inability to mount a physiological stress hormone response. The deficiency of growth hormone did not require replacement.

A broad diagnostic approach should always be employed when managing hyponatremia, and a high index of suspicion is required to diagnose adrenal insufficiency which tends to present with subtle, nonspecific symptoms. Empty sella may not be as rare as previously thought and requires careful assessment of associated neurologic and endocrine manifestations.

AUTHOR CONTRIBUTIONS
Dr. Siehoon Lah conceptualized, provided the methodology, investigated, involved in data curation, visualized, administered the project, wrote the original draft, reviewed, and edited the manuscript. Dr. Almas Wahab conceptualized, provided the methodology, investigated, provided the resource, reviewed and edited the manuscript. Dr. Ammar Wakil conceptualized, provided the methodology, investigated, provided the resource, reviewed and edited the manuscript, and supervised the manuscript.

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CONFLICT OF INTEREST
All authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT
Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

CONSENT
Written consent has been obtained from the patient whose clinical information is discussed in this paper.

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