Hyponatremia after anticoagulant treatment: a rare cause of adrenal failure

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Summary
A 69-year-old male was admitted for severe hyponatremia disclosed after an accidental fall. He was anticoagulated from 2 months after the implantation of a biologic aortic valve prosthesis. The work-up disclosed adrenal failure and MRI showed bilateral adrenal hemorrhage. Clinical picture and lab parameters normalized quickly after the appropriate replacement treatment. Anticoagulation excess should be added to the list of drugs potentially causing hyponatremia.

Background
Hyponatremia is a frequent event in elderly inpatients that requires a complete workup for the establishment of diagnosis and the start of an appropriate causal treatment (1). In the management of hyponatremia, it is of utmost importance to discriminate the time course, i.e. an acute vs chronic onset, and then to avoid two main errors: a delay in treatment and an overzealous rapid correction, causing hyponatremic encephalopathy and osmotic demyelination syndrome, respectively, both with an ominous prognosis (2, 3).

Case presentation
A 69-year-old male arrived in ER after an accidental fall, without losing consciousness, with head trauma and an ear wound.

Past history was remarkable for two aspects. An MRI performed a few months before, following abdominal pain, had shown a small pancreatic lesion, which was proposed for radiologic follow-up within 6 months by the oncologist and surgeon consultants. Two months before the patient had been submitted to cardiac surgery for severe aortic stenosis. A biologic valvular prosthesis had been implanted and oral anticoagulation (OAC) had been started. Notably hyponatremia was reported at discharge (122 mM/L, nv 132–145) but no indication had been given. During the following rehabilitation period, the patient complained anorexia, fatigue, progressive weight loss and depression. Serum sodium was unchanged.

Physical examination at ER disclosed poor clinical conditions, mental confusion, pallor and arterial hypotension (80/60 mmHg).

Learning points:
• Hyponatremia requires a complete and timely workup in order to start an appropriate treatment for the improvement of clinical conditions.
• History is crucial: a detailed list of drugs potentially causing hyponatremia should be collected. Anticoagulants should be added to the list, mostly in the event of excessive anticoagulation.
• Intra-adrenal hemorrhage is a rare cause of hyponatremia and adrenal failure.
• The ACTH test is still the gold standard for the diagnosis of hypoadrenalism.
Lab parameters at ER disclosed (Table 1): severe hyponatremia (114 mM/L, nv: 132–143), hyperkalemia (6.05 mM/L, nv: 3.4–5.2), low-grade renal failure (serum creatinine: 1.28 mg/dL, nv: 0.5–1.1; urea: 60 mg/dL, nv: 18–48), INR 4.5 (therapeutic target 2–3). Brain CT did not disclose any bleeding or expansive lesions, but old ischemic lesions (in the insular region bilaterally and in the subcortical posterior right area). The patient was admitted.

Hypopituitarism was hypothesized, prompting evaluation of serum cortisol at 12 pm (0.6 µg/L, nv at 07:00–10:00 h: 0.62–1.8) and FT4 (16.2 ng/L, nv: 9.2–17). Fluid resuscitation and hydrocortisone, 100 mg iv, were administered for persistent hypotension. The following morning, serum sodium was increased up to 118 mM/L (+4 mM/L). Serum cortisol was again assayed at 08:00 h (0.6 µg/L) and the patient was referred to the endocrinology ward during the afternoon of Friday.

As FT4 and cortisol levels apparently ruled out hypopituitarism, an ACTH test was planned for the next Monday and fluid restriction was started. After 48 h, it was unsuccessful. Abdomen MRI was performed to evaluate the known pancreatic lesion and rule out a paraneoplastic SIAD. No change was shown at the pancreatic level but hyperintense T1-weighted lesions were disclosed in both the adrenals, consistent with bleeding (Fig. 1, right adrenal size: 24 × 10 mm; left adrenal size: 14 × 15 mm).

Increased ACTH and renin levels were disclosed (1297 ng/L, nv: 7–63; and 309.2 mU/L, nv: 2.8–39.9, in recumbent position, respectively) and the peak cortisol level after ACTH 1 µg iv (0.66 µg/L, nv >1.8) pointed to adrenal failure.

A diagnosis of primary hypoadrenalism due to bilateral adrenal bleeding during OAC was made. The OAC was withdrawn in agreement with the cardiac surgeon because it was no longer indicated and specific treatment was started with cortisone acetate (25 + 12.5 mg/day) and fludrocortisone (0.1 µg/day).

ACTH test after 6 months showed the worsening of hypoadrenalism (peak cortisol levels: 0.05 µg/L).

Discussion

Hyponatremia is a frequent and underestimated event in elderly patients admitted to ER (1). It induces clinical pictures that are often puzzling, attributed to depression or degenerative vascular brain alterations. It is thus essential to draw a comprehensive diagnostic framework that is a prerequisite for the set up of an appropriate treatment capable of improving dramatically the clinical picture (2). The combination of hyponatremia and hyperkalemia as in this case, should point strongly to hypoadrenalism. Physicians taking care of the patient at first were diverted towards alternative diagnoses, such as hypopituitarism and SIAD (the latter due to the known undiagnosed pancreatic lesion). Both should have been considered in a lower position in the ranking order of probability and were eventually ruled out.

Table 1  Changes in sodium, potassium and cortisolemia values over time.

| Time                | Na (mM/L) | K (mM/L) | Cortisol (µg/L) | ACTH (ng/L) | FT4 (ng/L) |
|---------------------|-----------|----------|-----------------|-------------|------------|
| At arrival in ER    | 114       | 6        | 0.6             | 1297        | 16.2       |
| After hydrocortisone 100 mg | 118       | 6        | 0.6             | 1297        |            |
| At discharge        | 136       | 4.5      | 0.05            | 58          |            |
| After 2 months      | 139       | 4.5      | 0.05            | 58          |            |

Figure 1
Hyperintense T1-weighted lesions disclosed in both the adrenals, consistent with bleeding, disclosed by abdomen MRI.
This case report shows that OAC (or better its excess, causing intra-adrenal bleeding) should be added to the known causes of hyponatraemia in the elderly, sometimes concomitantly present, such as drugs (anti-depressant, carbamazepine, diuretics, ACE-inhibitors, desmopressin, cyclophosphamide, carbamazepine, phenothiazines), low-sodium diet, excessive water intake and endocrine diseases (hypothyroidism and hypoadrenalism).

At variance with other iatrogenic causes of hyponatraemia, bilateral adrenal hemorrhage, which is a well-known cause of adrenal failure, is irreversible (4, 5, 6, 7, 8, 9). The vascular anatomy of the adrenal gland, with a plexus of many arterioles and venules, draining into a single large vein susceptible to outflow obstruction, is believed to make the gland particularly prone to hemorrhagic infarction after central vein thrombosis. Thrombosis is a frequent cause of bleeding in cases of antiphospholipid antibody and heparin-induced thrombocytopenia. Rarely, bilateral bleeding occurs only in the setting of anticoagulation, with or without underlying adrenal masses. Adrenal insufficiency becomes clinically relevant when approximately 90% of the adrenal cortex has been destroyed. The repetition of the dynamic test to evaluate cortisol response to ACTH administration could thus be viewed as redundant in such a case. Furthermore, it is important to stress that OAC in our patient was no longer indicated and its withdrawal should not be regarded as the rule after adrenal bleeding.

We want to underline that hypoadrenalism is not ruled out by apparently normal cortisol levels (as the misleading value found at midnight in this patient and causing a delay in the diagnosis) during a powerful stress such as that experienced in the course of an acute disease. It is essential to maintain a high index of suspicion and to perform an evaluation of the entire pituitary–adrenal axis. The additional assay of ACTH levels can add useful information. The ACTH test that is still the gold standard for the diagnosis of hypoadrenalism is warranted whenever cortisol levels are in a grey area, requiring thus a more sophisticated diagnostic approach. On the contrary, it should be regarded as ancillary if morning cortisol level is very low. The error to avoid is to postpone the start of a life-saving glucocorticoid treatment until the test has been performed (or even worst to wait for its results).

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
Written informed consent has been obtained from the patient for publication of the submitted article. Authors must also provide a signed copy of our consent form.

Author contribution statement
B Z and R C were the physicians taking care of the patient, R A wrote the paper.

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