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THE NEVER-ENDING STORY OF HYPONATREMIA: A CURRENT PROBLEM TO OVERCOME

Benedetta Marigliano[1], Luigi Scuro[2]

[1] Facoltà di Medicina e Chirurgia, Università Cattolica del Sacro Cuore, Rome, Italy
[2] UOC Pronto Soccorso e Medicina d'Urgenza, Azienda Ospedaliera San Camillo – Forlanini, Rome, Italy

Corresponding author: Benedetta Marigliano **e-mail:** benemarigliano@hotmail.com

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ABSTRACT

Hyponatremia is a common complication in patients undergoing neurosurgery. If undiagnosed, it has a negative prognostic impact. The two dominant causes of refractory hyponatremia include syndrome of inappropriate ADH secretion (SIADH) and cerebral salt wasting syndrome (CSWS). Discrimination between the two types of disease is not always obvious. We present a case of undiagnosed chronic hyponatremia caused by CSWS after neurosurgery, which not only resulted in a longer hospital stay but also slowed the patient's postoperative recovery. Meticulous clinical evaluation and the performance of appropriate laboratory tests are therefore essential not only for decisive treatment, but also for the establishment of comprehensive diagnostic algorithms that allow timely diagnosis and decisive therapy.

KEYWORDS

Hyponatremia, syndrome of inappropriate ADH secretion, cerebral salt-wasting syndrome

LEARNING POINTS

- The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and cerebral salt-wasting syndrome (CSWS) are in general associated to refractory hyponatremia especially in patients with neurologic disorders.
- Extracellular fluid (ECF) assessment is the key to distinguish between SIADH and CSWS.
- Nevertheless, measurement of the ECF volume is not sufficient to determine the correct etiology and more established diagnostic algorithms are required.

INTRODUCTION

Hyponatremia is the most common electrolyte disorder encountered in the clinical setting and is a common complication in patients undergoing neurosurgery. Hyponatremia results in higher mortality, readmission rates and longer hospital stay[1]. Among the broad etiological spectrum, the two dominant causes include the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and the cerebral salt wasting syndrome (CSWS) that occur more frequently in response to subarachnoid haemorrhage and brain injury[2]. Both conditions are typical syndromes responsible for refractory hyponatremia in patients with neurological problems. It is often difficult to distinguish between the two types of disease and as to date there is no

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effective and reliable method to differentiate between them, SIADH and CSWS often remain undiagnosed. In both there is low serum osmolality, increased urinary sodium, osmolality and volume with normal thyroid and adrenal function. Accurate assessment of extracellular fluid (ECF) volume is the key to distinguishing the two types. We present a case of undiagnosed chronic hyponatremia caused by CSWS after neurosurgery led to a longer hospital stay and a slower postoperative recovery for the patient.

CASE DESCRIPTION

A 75-year-old woman with dyslipidaemia and hypothyroidism under replacement therapy was admitted to our emergency department for fever and intractable vomiting. She had recently undergone removal of a meningioma of the tuberculum sellae, with sequelae of amaurosis on the left, visual impairment on the right, and gait ataxia. After neurosurgery, she was transferred to a rehabilitation centre where she developed mild hyponatremia and recurrent febrile episodes, in the absence of elevated procalcitonin and C-reactive protein-(CRP) levels, and a urinary infection treated with antibiotic therapy guided by the antibiogram.

In the emergency room, she underwent laboratory and instrumental tests that showed normal values of creatinine (0.44 mg/dl), CRP (0.11 mg/dl), Hb (13.9 g/dl), moderate hypokalaemia (2.46 mEq/l) and hyponatremia (128 mEq/l), a high N-terminal pro b-type natriuretic peptide (NT proBNP) level (291 pg/ml), neutrophilic leucocytosis (GB 18850 mm^3), and a urinary specific gravity (SG) of 1006 with an alkaline pH in the absence of nitrite on dipstick examination.

Chest and brain imaging ruled out an acute emergency, thus leading to her admission to the emergency medicine department. At the time of admission to the ward, the patient appeared alert, cooperative with normal vital parameters except for a persistent fever (37.3°C) and polyuria with a urine volume of up to 7 liters per day. Diabetes insipidus was ruled out by an endocrinologic evaluation. Given the history of recent neurosurgery, the reported frequency of urination and the intense thirst during the previous rehabilitation stay (which would already suggest plasma volume contraction and polyuria, not demonstrable however, as there was no mention of this in the discharge letter), persistent hyponatremia, persistent spot natriuresis >100 mEq/l (with values up to 120 mEq/l), urinary osmolarity > 100 mOsm/l (given indirectly on urinary SG values), and persistent hypouricemia (i.e., 1. 5 mg/dl) CSWS was hypothesized to be the unifying diagnosis. Free fractions (fT3 7 pmol/l, fT4 15 pmol/l) and thyroid stimulating hormone (TSH) (2 mU/l), cortisol (22 mcg/dl) and adrenocorticotropic hormone (ACTH) (24 pg/ml) were also in the normal range, corroborating the diagnosis.

With isotonic saline solution and piperacillin-tazobactam antibiotic therapy, a gradual improvement in the patient's condition, with regression of polyuria followed by a maintenance of optimal water balance. She was asymptomatic when discharged, with hemodynamic and respiratory compensation, restoration of bladder continence and resumption of the remaining basic activities of daily living.

DISCUSSION

Hyponatremia reflects an excess of total body water (TBW) relative to the total body sodium content. Total body sodium content is influenced by ECF volume, therefore, hyponatremia must be considered along with the volume status (hypovolemia, euvolemia, and hypervolemia) taking into account that sometimes there could be pseudohyponatremia. The latter is caused by an excess of other plasma substances (i.e., glucose, mannitol, glycerol, lipids) rather than a water-sodium discrepancy. In fact, serum sodium concentrations decrease by 1.6 mEq/l for every 100 mg/dl increase in serum glucose concentration above normal[2].

Hyponatremia occurring after neurosurgery is usually mild and appears on postoperative day 7, resolving spontaneously within 5 days[2]. Patients undergoing neurosurgery are always prone to develop hyponatremia, especially those with craniopharyngioma and Cushing's disease, which occurs in up to 35% of cases[3]. Older age (>70 years), female sex, and tumor size have been identified as predictors of delayed symptomatic hyponatremia, as occurred in our case. There are no conclusive data as regards the factors predicting this manifestation. It is most likely that an overload of hypotonic or isotonic solutions during perioperative period may contribute to its development. Both CSWS and SIADH are characterized by hyponatremia, low osmolality (<275 mOsm/l), high urine osmolality (>100 mOsm/l), urine sodium > 20 mEq/l, and low serum uric acid. ECF volume assessment is generally the key distinguishing factor. Patients with CSWS have markedly elevated urine volume and sodium excretion (because of natriuresis) compared with patients with SIADH (which is due to excessive ADH activity) although clinical signs of dehydration (e.g., postural hypotension, increased heart rate, and mucosal dryness) are not always helpful in diagnosing CSWS with certainty, considering the errors in subjective assessments[3]. Besides, short-term infusion of isotonic saline, which should improve serum sodium in CSWS, may be insufficient and hypertonic saline, possibly combined with fludrocortisone in refractory cases, may be required[4].

SIADH is attributed to excessive vasopressin release or gain of function mutations in the V2 vasopressin receptor in the renal collecting tubules[5]. It is defined as a less than maximally diluted urine in the presence of hyponatremia without volume depletion or overload, emotional distress, pain, diuretics, or other drugs that stimulate vasopressin secretion (e.g., carbamazepine, antipsychotics, aspirin, ibuprofen) in patients with normal cardiac, hepatic, renal, adrenal, and thyroid function[3]. Patients with SIADH are euvolemic or slightly hypervolemic. Treatment of SIADH involves fluid restriction according to the sodium level: if the plasma sodium level is between 130 and 134 mEq/l, <1200

ml/day, if it is between 126 and 130 mEq/l, < 800 ml, and <600 ml whenever the sodium level is <125 mEq/l[6].

CSWS has been proposed as an important cause of hyponatremia in patients with acute or chronic damage of the central nervous system. Specifically, Bitew et al., demonstrated that impaired sympathetic neural input to the juxtaglomerular apparatus may reduce proximal tubule sodium, urate, and water reabsorption and decrease renin and aldosterone release while Berendes et al., proposed the "natriuretic peptide theory" indicating how atrial and brain natriuretic peptides (ANP and BNP) may play important roles in increasing the sodium excretion and urine volume[7,8]. Though natriuretic peptides (especially NT-proBNP) may be a contributing factor for CSWS, they cannot serve as a diagnostic marker because of their short half-life and presence in many other settings (such as cardiopulmonary diseases and in chronic renal failure). In patients with hypovolemia a urine sodium level > 20 mEq/l may suggest, other than CSWS, a renal fluid loss secondary to mineralocorticoid deficiency or to a "salt-losing nephropathy". The latter category includes an inaccurately defined group of intrinsic renal disorders with primary renal tubular dysfunction (i.e., interstitial nephritis, medullary cystic disease, urinary tract obstruction, and polycystic kidney disease)[4]. Treatment in CSWS involves solute and fluid replacement. For sodium values >130 mEq/l a specific treatment is not required, while between 125-130 mEq/l, sodium replacement can be carried out by administering isotonic saline solution (0.9%) or salt in pills (1-3 g/day)[6]. In some cases, hyponatremia may be due to mixed SIADH and CSWS. In fact, elevated ADH levels can cause SIADH, or they can be a consequence of extracellular volume depletion and hypoosmolality caused by CSWS[6].

Treatment requires proper diagnosis. In the absence of clear clinical and biochemical signs performing a furosemide test can help differentiate between SIADH and CSWS furosemide (or any other loop diuretic), specifically, when added to the treatment when sodium concentrations in SIADH are <128 mEq/l, in symptomatic patients, favour a return to normal sodium serum levels, but this does not occur in CSWS[6]. In addition, studies have found that hypouricemia worsens in CSWS whereas normalizes in SIADH, according to unknown mechanisms[3]. Elevated levels of fractional excretion (FE) urate are >11% in both syndromes and normalise after correction (normal values 4-11%) in SIADH while they remain >11% in CSWS[3]. FE urate can be calculated with simultaneous creatinine and urate blood and urine sampling using the formula of Maesaka et al.[9]: (urine urate/serum urate)/(urine creatinine/serum creatinine)×100. Therefore, calculating the FE urate before and after treatment may be a feasible method to identify the aetiology of undiagnosed refractory hyponatremia.

In cases of acute hyponatremia (lasting less than 48 hours), symptoms appear when severe (<120 mEq/l). In contrast, in chronic cases (hyponatremia lasting more than 48 hours), which have minimal neurological symptoms, there is a low risk of complications from hyponatremia itself. For both syndromes, hypertonic saline solution (3%-containing 513 mEq sodium/l) will be restricted to those situations where plasma sodium concentrations are <120 mEq/l following the Adrogué Madias formula. The latter considers the desired change in sodium multiplied for the total body water (TBW) (0.6 × body weight in kg in men and 0.5 × body weight kg in women)[10]. Lasting correction depends on successful treatment of the underlying disorder. Strict monitoring of electrolytes is fundamental since a rapid correction may cause serious neurological complications such as demyelination. To avoid pontine or extrapontine myelinolysis (especially in patients suffering from malnutrition or alcoholism) the rate of sodium correction should not exceed 8 mEq/l over the first 24 hours[2]. Another recommendation includes administration of desmopressin 1 to 2 mcg every 8 hours concurrently with hypertonic saline, because desmopressin prevents an unpredictable water diuresis that can follow the abrupt normalization of endogenous vasopressin that can occur as the underlying disorder causing hyponatremia is corrected. After the sodium has been corrected at the appropriate rates for 24 hours, desmopressin can be stopped. Fludrocortisone, due to its mineralocorticoid action, may be beneficial in refractory cases at doses of 0.1-0.4 mg/day[4]. In situations of resistant hyponatremia, a vasopressin receptor antagonist (i.e., conivaptan, tolvaptan) can be used in hospitalized patients for less than 30 days (due to potential liver and renal toxicity with chronic use), causing effective water diuresis without loss of urinary electrolytes[3]. In any case, fluid restriction combined with increased solute intake (e.g., salt tablets or oral urea) has also been found to be effective in chronic conditions.

CONCLUSIONS

In our patient, the diagnosis was made retrospectively and was based on clinical, biochemical data and the patient's response to treatment. While it is true that hyponatremia can be the internist's grave, it is also equally true that meticulous clinical evaluations and appropriate laboratory testing dramatically reduce the likelihood of error, allowing a targeted diagnosis necessary for decisive treatment. Currently, there are still no straightforward diagnostic algorithms validated by evidence-based medicine to clearly distinguish a SIADH from a CSWS. Thus, there is a need to design more prospective clinical trials directed at clearing those doubts that do not allow an accurate diagnosis because of the prognostic implications related to improper therapeutic management.

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