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A case of hyponatremia caused by central hypocortisolism

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SUMMARY

Background A 43-year-old woman was referred to the Psychiatric Unit of the University of Florence Hospital, 1 year after the development of a clinical picture characterized by nausea, hyporexia, muscle weakness, insomnia, weight loss, amenorrhea and severe depression. These clinical manifestations had started 2 months after delivery of her first child. Initial laboratory investigations revealed hypoglycemia and hyponatremia. The patient was, therefore, transferred to the Endocrine Unit of the same hospital for further evaluation of the case.

Investigations Physical examination to evaluate extracellular volume status, standard laboratory investigations, and evaluation of plasma and urinary osmolality and urinary sodium excretion. Basal and dynamic evaluation of anterior pituitary function and a pituitary MRI were also performed.

Diagnosis Hyponatremia caused by central hypocortisolism (isolated adrenocorticotropic hormone deficit).

Management Glucocorticoid therapy (25 mg cortisone acetate tablets, 1.5 tablets per day).

KEYWORDS depression, extracellular volume status, hypocortisolism, hyponatremia, lymphocytic hypophysitis

CME

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THE CASE

In March 2005, a 43-year-old woman was referred to the Psychiatric Unit at the University of Florence Hospital. She reported that since June 2004, 2 months after her first delivery, she started to suffer from nausea, severe hyporexia, muscle weakness and insomnia. Her weight was then 62 kg (BMI 22.8 kg/m^2). A few months later, she began to suffer from severe depression, a marked diminution of interest in most activities, diminished ability to concentrate, profound loss of energy, loss of sexual desire, feelings of worthlessness, and subjective chills without fever. She was still amenorrheic. She had no family or personal past history for Axis I clinical syndromes of mental dysfunction.

At admission, her weight was 47 kg (BMI 17.2 kg/m^2). She was not taking any medication. Diagnostic and Statistical Manual of Mental Disorders IV criteria for major depressive episode were fulfilled. The main values for routine laboratory investigations revealed low fasting glucose levels (2.8 mmol/l; normal range 3.6–6.1 mmol/l) and sodium levels (125 mmol/l; normal range 135–146 mmol/l). The patient was transferred to the Endocrine Unit of the same hospital. Clinical examination revealed normal extracellular volume status (EVS) (i.e. normal skin moisture, no distended or flat veins, no sunken eyes), hypotonic and hypotrophic limb muscles, no melanodermia, moderately diminished axillary and pubic hair, blood pressure 100 over 65 mmHg without relevant postural changes, pulse rate 78 beats per minute. There were no abnormal neurologic findings.

Baseline evaluation confirmed the presence of hypoglycemia and hyponatremia (Table 1). Dynamic testing for anterior pituitary hormone reserve revealed a normal TSH, follicle-stimulating

Table 1 The patient's initial laboratory results after transfer to the Endocrine Unit.

Laboratory measurement	Results	Normal range
Glucose	2.7 mmol/l	3.6–6.1 mmol/l
Serum sodium	127 mmol/l	135–146 mmol/l
Serum urea	7.2 mmol/l	3.6–18.0 mmol/l
Hemoglobin	11.0 g/dl	12–16 g/dl
Hematocrit	30.5%	36–46%
Urinary sodium	77 mmol per day	50–200 mmol per day
Serum creatinine	53 μmol/l	53.0–132.6 μmol/l
Serum uric acid	0.083 mmol/l	0.21–0.38 mmol/l
Serum potassium	3.8 mmol/l	3.5–5.3 mmol/l
Serum insulin	<0.2 mIU/l	3–17 mIU/l
Plasma renin activity	0.59 μg/l/h	1.0–4.5 μg/l/h
Plasma osmolality	272 mOsm/kgH_2O	285–295 mOsm/kgH_2O
Urine osmolality	563 mOsm/kgH_2O	300–1,100 mOsm/kgH_2O
Follicle-stimulating hormone	9.77 IU/l	3–9 IU/l (early follicular phase)
Luteinizing hormone	18.28 IU/l	0.5–9.0 IU/l (early follicular phase)
17β-estradiol	58 pmol/l	70–220 pmol/l (early follicular phase)
TSH	2.93 mIU/l	0.25–3.5 mIU/l
Free T_4	10.34 pmol/l	10.3–19.4 pmol/l
Free T_3	6.02 pmol/l	3.5–6.4 pmol/l
Antithyroperoxidase antibodies	350 IU/ml	<35 IU/ml
Prolactin	2,535 mIU/l[a]	72–504 mIU/l[a]
Growth hormone	0.90 μg/l	<4.0 μg/l
Insulin-like growth factor 1	41 nmol/l	13–65 nmol/l
Adrenocorticotropic hormone	<5.0 ng/l	9–52 ng/l
Serum cortisol	6 nmol/l	160–690 nmol/l
Adrenocorticotropic hormone[b]	<5.0 ng/l	9–52 ng/l
Serum cortisol[b]	10 nmol/l	160–690 nmol/l

[a]To convert mIU/l to pmol/l, multiply by 2.043. [b]Hormonal assessment after 1 year of follow-up.

hormone, luteinizing hormone and growth hormone response (Figure 1A–C). Conversely, no changes in adrenocorticotropic hormone (ACTH) and serum cortisol levels were observed after corticotropin-releasing hormone stimulation (Figure 1D). In agreement with the psychiatrist's suggestion, no insulin tolerance test was performed, because of the very severe psychiatric condition of the patient. MRI of the head showed a thickened (2.7 mm) pituitary stalk. Glucocorticoid therapy was started (one 25 mg cortisone acetate tablet at 0800 h, and half of a 25 mg tablet at 1600 h) and within 2 days, serum sodium levels gradually increased and ultimately returned to normal (136 mmol/l). After 1 year of follow-up, the patient had completely recovered from depression, her muscle tone and strength dramatically improved, a 10 kg weight gain was observed and regular menses returned. At that time, a repeat hormonal assessment (performed off therapy) confirmed the previous diagnosis (Table 1) and, therefore, glucocorticoid replacement treatment was continued. All the patient's other anterior pituitary hormones were within the normal range.

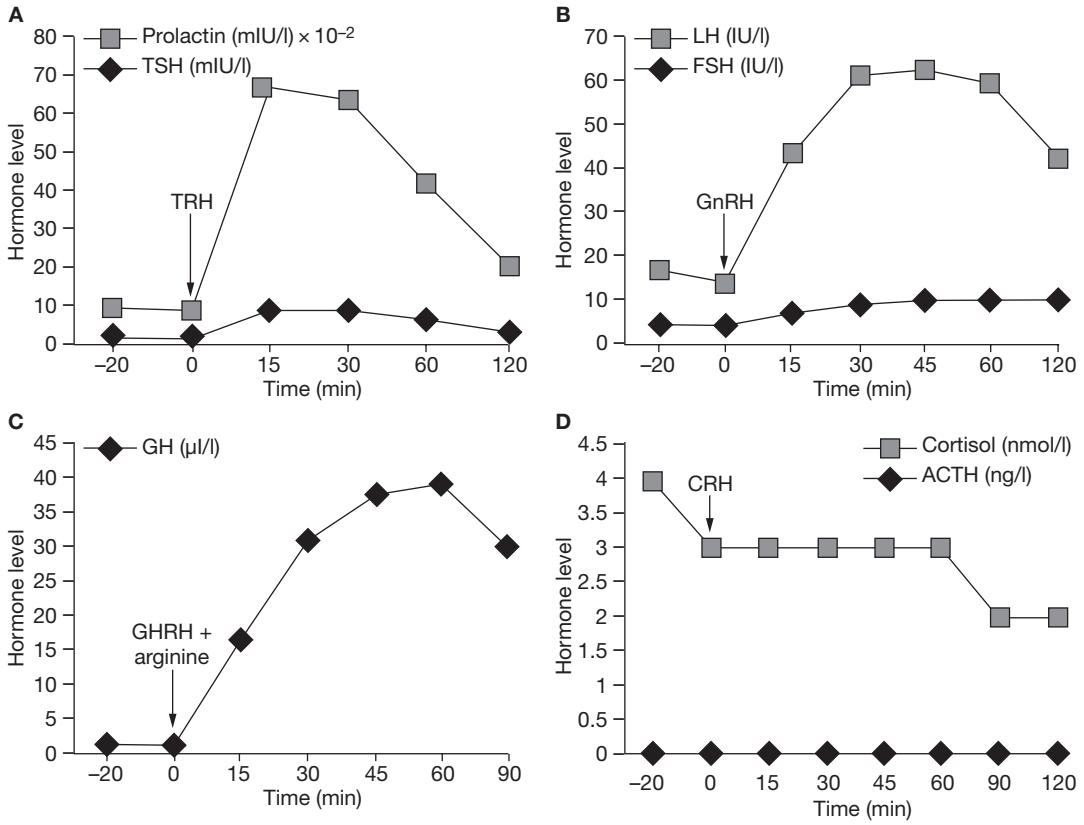

Figure 1 Results of dynamic tests for evaluation of pituitary hormones. (**A**) Response of TSH and prolactin after intravenous administration of 200 µg TRH. To convert prolactin values to pmol/l multiply by 2.043. (**B**) Response of FSH and LH after intravenous administration of 100 µg GnRH. (**C**) Response of GH after intravenous administration of 1 µg/kg GHRH plus 0.5 g/kg arginine. (**D**) Plasma levels of ACTH and cortisol after intravenous administration of 100 µg CRH. Abbreviations: ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; FSH, follicle-stimulating hormone; GH, growth hormone; GHRH, growth-hormone-releasing hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; TRH, TSH-releasing hormone.

DISCUSSION OF DIAGNOSIS

Hyponatremia, defined as a decrease in serum sodium concentration to below 135 mmol/l, is one of the most common electrolyte disorders, and affects up to 15% of all hospitalized patients in Western countries.[1] Hyponatremia can be divided into three forms on the basis of plasma osmolality: hypotonic, nonhypotonic (essentially represented by pseudohyponatremia, i.e. hyponatremia in the presence of severe hyperlipidemia or paraproteinemia) and hypertonic (i.e. caused by hyperglycemia).

Hypotonic hyponatremia is the consequence of an excess of water in relation to total body sodium stores. Hypotonic hyponatremia results from depletion of total body sodium in excess of concurrent body water losses, or from dilution of total body sodium by increases in total body water.[2] Depending on the patient's EVS, hypotonic hyponatremia can be classified as one of three types: hypovolemic, hypervolemic and normovolemic (Table 2).[1]

Normovolemic hyponatremia, essentially represented by the syndrome of 'inappropriate' secretion of antidiuretic hormone (SIADH), accounts for about 60% of all cases of chronic hyponatremia (inappropriate because secretion occurs other than in response to plasma hyperosmolarity, arterial hypotension or hypovolemia). The diagnostic criteria for SIADH include urine osmolality higher than 100 mOsm/kg$H_2$0, initial renal sodium excretion higher than 30 mmol/l, absence of edema or volume depletion, and normal renal, adrenal and thyroid function.[3]

Normovolemic hyponatremia is also present in patients with secondary hypocortisolism, the clinical and biochemical features of which are hard to distinguish from those of SIADH.[4]

Table 2 Main causes of hypotonic hyponatremia.

Extracellular volume status		
Hypovolemia	**Normovolemia**	**Hypervolemia**
Gastrointestinal fluid loss	SIADH	Heart failure
Primary adrenal failure	Hypocortisolism	Cirrhosis
Salt-losing nephritis	Hypothyroidism	Nephrotic syndrome
Cerebral salt wasting	Primary polydipsia	Renal failure
Burns		
Diuretics		

Abbreviation: SIADH, syndrome of inappropriate antidiuretic hormone secretion.

Table 3 Drugs that can cause SIADH.

Action	Drugs
Stimulation of AVP release	Opiates Nicotine Tryciclic antidepressants Phenothiazines Haloperidol Oxytocin Dopamine agonists Methylenedioxymethamfetamine[a]
Direct renal effects, potentiation of AVP action, or both	Desmopressin NSAIDs
Mixed or uncertain action	ACE inhibitors Clofibrate Cyclophosphamide Colchicine Vincristine Carbamazepine, oxcarbazepine Clozapine Serotonin reuptake inhibitors Amiodarone

[a]MDMA, colloquially known as 'Ecstasy'. Abbreviations: ACE, angiotensin-converting enzyme; AVP, arginine vasopressin; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

In secondary hypocortisolism the main cause of hyponatremia seems to be an increase in arginine vasopressin (AVP) production, which is mainly caused by loss of the tonic inhibitory effect of endogenous cortisol on AVP secretion;[5] other factors—such as nausea and hypoglycemia—can also exert a similar effect.[4] It has been demonstrated that hypocortisolism results in overexpression of aquaporin-2 water channels, which results in decreased water excretion by the kidney.[6]

Hypothyroidism is another possible cause of normovolemic hyponatremia. The decreased cardiac output and effective arterial blood volume (EABV) that occur in patients with hypothyroidism reduce the glomerular filtration rate and, therefore, cause an increase in proximal tubular water reabsorption; moreover, decreased EABV stimulates AVP secretion, which further promotes water reabsorption.[7]

This patient's biochemical features (normal serum levels of creatinine and urea, low serum levels of uric acid and low hematocrit) and clinical features (absence of edema or signs of volume depletion) were in agreement with a diagnosis of normovolemic hyponatremia; her plasma and urine osmolality values and sodium urinary excretion levels were consistent with a diagnosis of SIADH. This syndrome is often caused by tumors, drugs (Table 3), central nervous system and pulmonary disorders;[8] nevertheless, in this patient the association of gastrointestinal symptoms, amenorrhea, weight loss, and in particular hypoglycemia, were suggestive of hypocortisolism; her psychiatric symptoms could also be in agreement with this diagnostic hypothesis. In fact, hypocortisolism caused by reduced bioavailability of cortisol or impaired glucocorticoid responsiveness has been found to be associated with depression in a number of instances.[9]

This patient's clinical features (presence of normovolemia and lack of skin pigmentation) and biochemical features (normal serum levels of potassium and urea and low levels of plasma renin activity) indicated that a diagnosis of primary adrenal failure was unlikely, whereas secondary hypocortisolism was considered a likely diagnosis. An extensive baseline and dynamic evaluation of her pituitary function revealed the presence of an isolated ACTH deficit. This rare condition is often associated with lymphocytic hypophysitis, a suggested autoimmune disorder,[10] which has particularly been reported in women.

A diagnosis of lymphocytic hypophysitis can only be established by histologic examination, but several features of the patient supported this hypothesis—a close temporal relationship between clinical manifestation and pregnancy, the radiologic finding of pituitary stalk enlargement,[11] the presence of hormonal pituitary abnormalities (such as hyperprolactinemia, but in particular an isolated ACTH deficiency) and the association with autoimmune thyroiditis (Table 1). The natural history of lymphocytic hypophysitis might be variable, and spontaneous remission might be observed, but a careful follow-up is required in order to identify any abnormalities in other pituitary hormones.[10]

A further aspect that should be considered in this patient is the presence of hypergonadotropic amenorrhea. In most cases, amenorrhea that

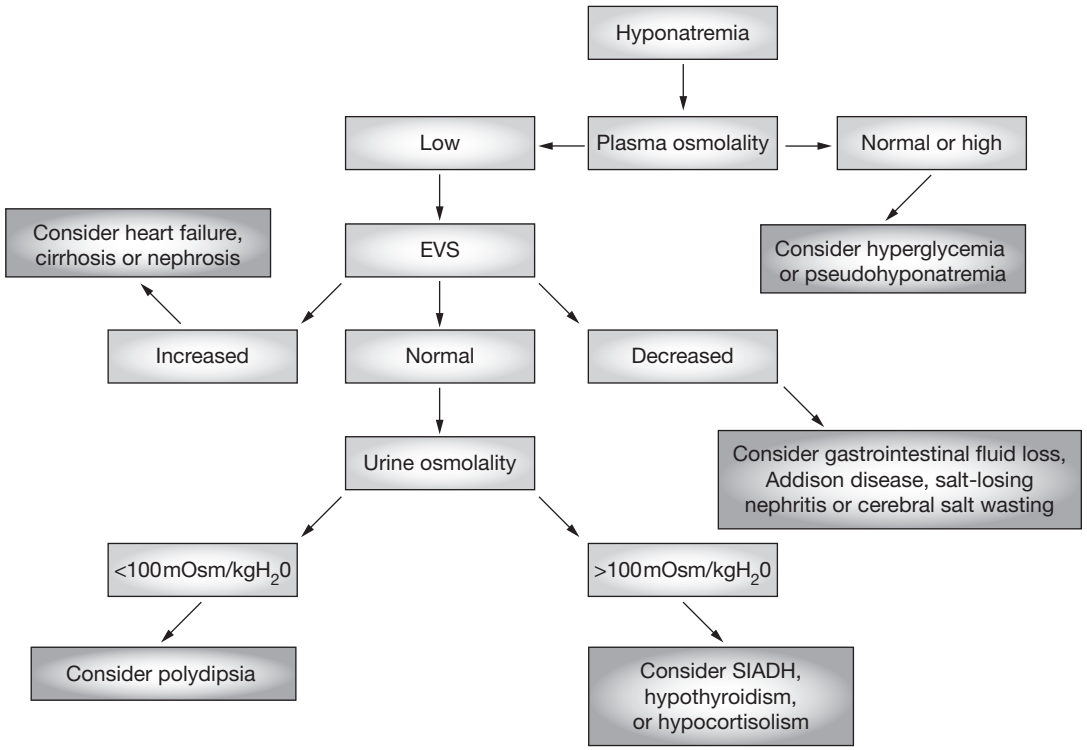

Figure 2 Flowchart of the diagnostic work-up for hyponatremia. Abbreviations: EVS, extracellular volume status; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

occurs during chronic disease is characterized by low levels of gonadotropins. Hypocortisolism itself, however, might negatively affect ovarian function.[12] Cortisol has also been demonstrated to stimulate the secretion of estrogen and progesterone by granulosa cells.[13]

TREATMENT AND MANAGEMENT

As a general rule, the treatment of hyponatremia should be directed at the primary underlying disorder because such treatment might, in itself, correct the electrolyte imbalance. Thiazide diuretics and drugs that induce SIADH should be discontinued if possible, and hormone replacement therapy should be given to patients with suspected hypothyroidism or adrenal failure after hormonal evaluations have been performed.

Determination of EVS represents the first step in the evaluation of hypotonic hyponatremia (Figure 2). If the extracellular volume is expanded, the underlying disease should be identified if not previously known, and specific treatment should be started. A scheme for the initial approach to treatment of symptomatic and asymptomatic hyponatremic patients is summarized in Figures 3 and 4.

If hypovolemia is present, infusion of isotonic saline (0.9% NaCl) should be initiated, particularly in symptomatic patients, at an appropriate rate, to correct the estimated fluid and sodium deficit. Isotonic saline infusion is also appropriate for patients in whom it is initially difficult to distinguish between a hypovolemic and a euvolemic state, and this approach can also have diagnostic value—if euvolemic rather than hypovolemic hyponatremia is present, no improvement in serum sodium levels will be observed.[8]

If symptomatic, potentially life-threatening, euvolemic or hypervolemic hyponatremia is present, infusion of hypertonic saline (3% NaCl) should be considered. This approach, however, requires great caution, because severe side effects are possible (see below). Hypertonic saline is usually administered with furosemide (especially in hypervolemic patients), in order to limit expansion of the extracellular fluid volume that is induced by this treatment.[2] Moreover, diuresis induced by furosemide is characterized by renal excretion of free water rather than sodium, which favors the correction of hyponatremia.

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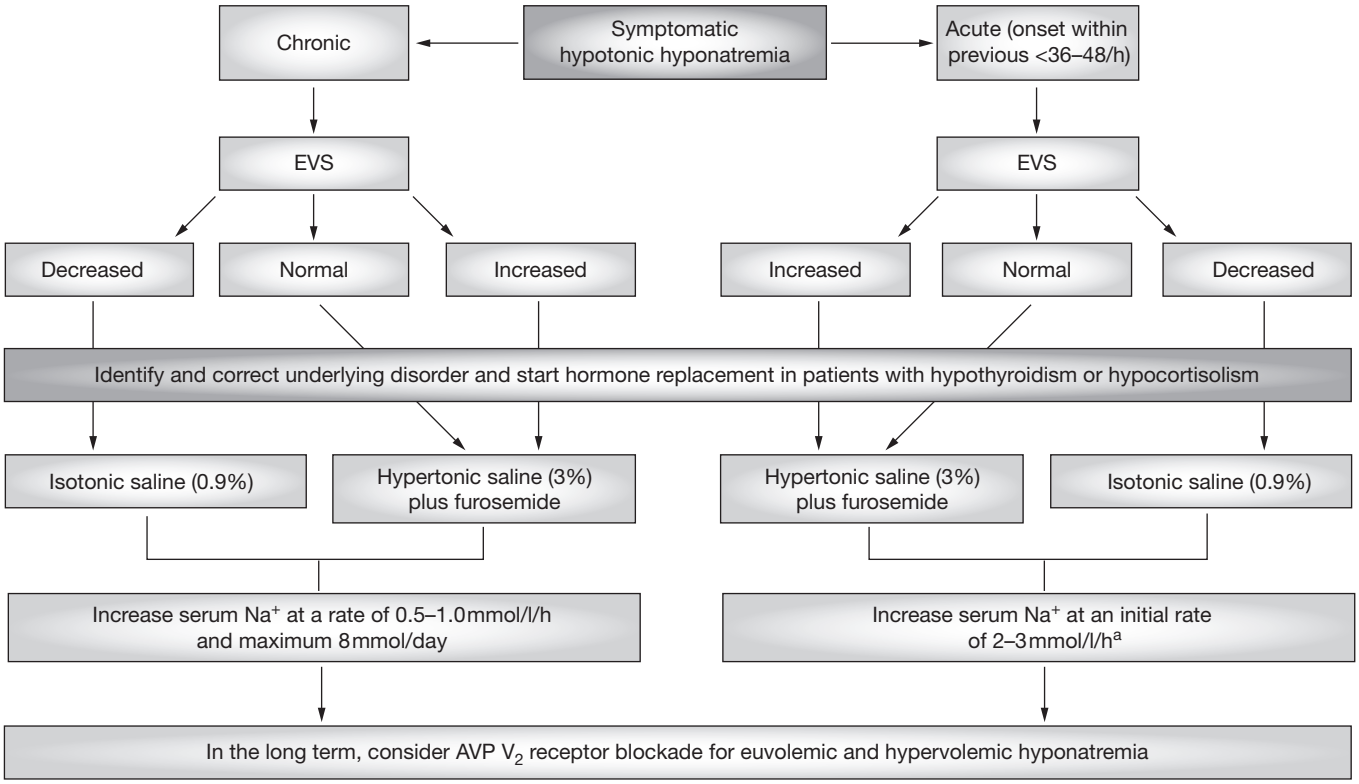

Figure 3 Schematic representation of the therapeutic approach for a patient with symptomatic hypotonic hyponatremia. [a]The initial rate of sodium correction of 2–3 mmol/l/h should be reserved for severely symptomatic patients (i.e. those with seizures or coma). Abbreviations: AVP, arginine vasopressin; EVS, extracellular volume status.

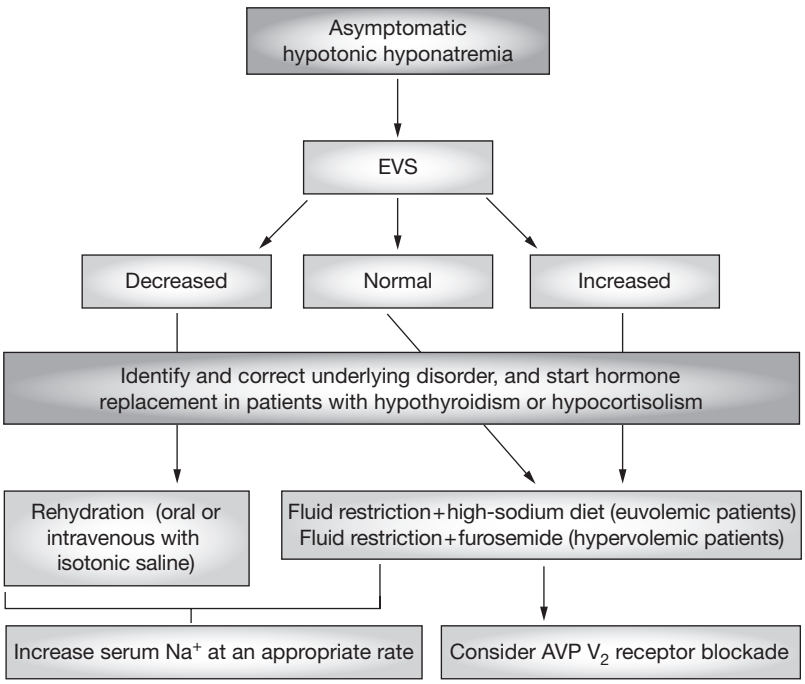

Figure 4 Schematic representation of the therapeutic approach for a patient with asymptomatic hypotonic hyponatremia. Abbreviations: AVP, arginine vasopressin; EVS, extracellular volume status.

A crucial point is the rate of correction of hypotonic hyponatremia. In chronic hyponatremia, a rapid increase in sodium levels puts the patient at risk for the development of cellular dehydration, and an extreme consequence might be central pontine myelinolysis (CPM). Most reported cases of CPM occurred after rates of correction higher than 12 mmol per day, but some cases have also occurred after correction rates of 9 mmol per day. Although other risk factors for CPM (such as malnutrition, hypokalemia or liver disease) were present in most of these cases,[14] it is recommended not to exceed a correction rate of 8 mmol per day. An initial hourly rate of correction of 0.5–1.0 mmol/l is usually recommended. Nonetheless, in patients with acute (onset within the past 36–48 h) and severely symptomatic hyponatremia (i.e. with seizures or coma) a more rapid initial correction at an hourly rate of approximately 2–3 mmol/l is strongly recommended, because these patients have a high risk of morbidity and death.[8]

Infusion of hypertonic saline should be stopped when the patient becomes asymptomatic, levels

Box 1 Formula for the management of hyponatremic patients.

$$\text{Change in serum } Na^+ = \frac{\text{Infusate } Na^+ - \text{serum } Na^+}{\text{Total body water} + 1}$$

- Change in serum Na^+ refers to the change after 1 l of any infusate
- Infusate Na^+ is 513 mmol/l with hypertonic saline (3% NaCl) infusion, and 154 mmo/l with isotonic saline (0.9% NaCl) infusion
- Serum Na^+ refers to Na^+ concentration of the patient's serum
- Total body water is calculated as a fraction of body weight (i.e. 0.6 and 0.5 in nonelderly men and women, and 0.5 and 0.45 in elderly men and women, respectively)

Modified with permission from Adroguè and Madias (2000).[2]

of serum sodium reach 120 mmol/l, or both. A formula to calculate the rate of saline infusion can be of help in the management of these situations (Box 1).

Fluid restriction represents the safe mainstay of management of asymptomatic hypervolemic and euvolemic hyponatremia.[1] In cases of SIADH, fluid restriction can be associated with a high-sodium diet (10 g per day orally).

AVP V_2 receptor blockade has been proposed as a promising alternative approach to treatment of euvolemic or hypervolemic hyponatremia. Selective V_2-receptor antagonists promote free-water excretion and sodium and potassium reabsorption in the kidney, which normalizes serum sodium levels and prevents the hypokalemia associated with loop diuretics. Tolvaptan—a novel V_2-receptor antagonist—seems to be more effective than fluid restriction for correction of euvolemic or hypervolemic hyponatremia, and does not cause an increase in adverse events.[15]

In this case hormonal replacement therapy with glucocorticoids represented the obvious therapeutic choice, and cortisone acetate was prescribed.

CONCLUSION

We reported the complex case of a 43-year-old woman with severe depression exacerbated by hyponatremia. The diagnostic work-up carried out illustrates the importance of identifying the etiology of an electrolyte imbalance in order to start the most appropriate treatment. We suggest that hypocortisolism should always be taken into consideration as a possible diagnosis in patients with normovolemic hyponatremia who have severe depression.

Competing interests
The authors declared they have no competing interests.

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