CASE REPORT

Early hyponatraemia after pituitary surgery: cerebral salt-wasting syndrome

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Abstract

Hyponatraemia is a common complication in patients undergoing neurosurgery. It can be caused either by the syndrome of inappropriate secretion of antidiuretic hormone or by the cerebral salt-wasting syndrome (CSWS). CSWS frequently occurs in patients suffering from subarachnoid haemorrhage and brain injury, but it is rare after pituitary tumour surgery. However, this diagnostic possibility should be considered as these disorders require specific treatment and have different prognoses.

In this article, we present a case of acute and early hyponatraemia caused by CSWS after pituitary tumour surgery. We also revise the aetiology, mechanisms, differential diagnosis and treatment of hyponatraemia after pituitary surgery.

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Case report

A 35-year-old woman presented with headaches and decreased visual acuity, which she had been experiencing for several months. She did not have any clinical manifestations of endocrine dysfunction and her baseline hormonal parameters were normal. The campimetry revealed minimum central vision in the superior nasal quadrant of the right eye and temporary hemianopsia in the left eye.

Nuclear magnetic resonance revealed a tumour of 4 cm in the pituitary with a central cyst which compressed the optic chiasm and invaded the cavernous sinuses. The patient underwent transsphenoidal surgery and the tumour was partially resected. No postoperative complications occurred and postoperative hormonal parameters were normal (i.e. thyroid hormones, 24-h urinary free cortisol and basal plasma cortisol, gonadotrophins, oestradiol, prolactin, growth hormone (GH) and insulin-like growth factor I). The anatomopathological examination confirmed pituitary adenoma with focal follicle-stimulating hormone positivity.

Ten months later, the patient underwent a new intervention due to the significant growth of tumoural rests. Hypotonic solution (i.e. infusate of 0.2% sodium chloride in 5% dextrose in water (1500 ml/day)) was administered in the first 48 h after surgery. Early baseline hormonal assessment did not show any deficit. The only postoperative complication was acute hyponatraemia with excessive natriuresis. At 48 h postsurgery, asymptomatic hyponatraemia (126 mEq/l, the normal

range being 135–145 mEq/l) with serum osmolality of 264 mOsm/kg (normal range 275–300 mOsm/kg) and elevated natriuresis (urine sodium 215 mEq/l, diuresis 3250 ml/24 h and urinary osmolality 706 mOsm/kg) were detected. Twenty-four hours later, the patient presented with nausea and vomiting; natraemia had decreased to 116 mEq/l, and natriuresis levels remained elevated (118 mEq/l, diuresis 2100 ml/24 h). The examination showed dry mucous membranes and slightly decreased skin turgidity; arterial systolic pressure was between 110 and 100 and diastolic pressure between 60 and 70 mmHg. No other symptoms of volume depletion were found. The patient was administered 3% hypertonic saline solution (31 ml/h for 2 days and then 15 ml/h). Natraemia levels rose to 124 mEq/l in 24 h; at this point, the saline solution was withdrawn and the patient was administered enteral salt supplementation (207 mEq/day) and fludrocortisone 0.1 mg/12 h. Despite the treatment, natraemia decreased to 118 mEq/l after 24 h. Perfusion with 3% hypertonic saline solution (31 ml/h) was resumed and the dose of fludrocortisone was increased to 0.1 mg/8 h. In 2 days, the patient was stabilised; plasma sodium and natriuresis levels were normal.

Table 1 shows the evolution of serum sodium, urine sodium levels, sodium balance and water balance.

Revision

Hyponatraemia is a common complication after pituitary tumour surgery and its incidence ranges from 1.8

Table 1 Evolution of hyponatraemia, urinary sodium levels and diuresis during the first 9 days of follow-up.

Biochemical data	Days from surgery								
	1st	2nd	3rd	4th	5th	6th	7th	8th	9th
Serum sodium (mEq/l)	141	126	116	119	122	124	118	123	133
Urinary sodium (mEq/l)	<20	215	128	138	105	189	–	112	72
Input sodium (mEq/day)	51	51	381	381	190	207	381	207	207
Sodium balance	Positive	Negative	Negative	Positive	Positive	Negative	–	Negative	Positive
Diuresis 24 h (ml)	1250	2150	3250	1450	1750	2150	1800	2350	1430
Water balance	Positive	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative

to 35% according to different studies (1, 2). The main cause is the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Exceptionally, cerebral salt-wasting syndrome (CSWS) has also been claimed as the cause of hyponatraemia after pituitary surgery, but few cases have been reported in the last 20 years (3–5).

Hyponatraemia may occur early during the first 24 h after surgery or at a later stage. It usually appears between 5 and 9 days after the intervention, reaching its maximum peak around the seventh day. On average, it resolves within 3–5 days. Occasionally, hyponatraemia occurs once the patient has been discharged, hence there is a need to inform the patient about its symptoms and to advise patients to get in touch with their physician should any symptoms appear. Nevertheless, hyponatraemia is usually mild; it goes unnoticed and resolves spontaneously (6).

There are no conclusive data as regards the factors predicting this disorder. A higher prevalence has been reported in patients with macroadenomas, in GH-producing tumours, and among female patients. The only certain predicting factor is the adrenocorticotrophin-secreting adenoma. In this case, hyponatraemia is related to adrenocortical insufficiency (2, 5–7).

The clinical manifestations of hyponatraemia depend on both its severity and its rate of development. The main clinical symptom is neurological dysfunction, which reflects the cerebral oedema secondary to plasmatic hypoosmolality. The rapid development of hyponatraemia, even when it is not severe, can cause symptoms, because of a failure of brain adaptation.

The aetiology of hyponatraemia after pituitary surgery is diverse. It is frequently caused by an overload of hypotonic or isotonic solutions during the perioperative period and also by an overdose of desmopresin acetate in a previous stage of diabetes insipidus.

SIADH and CSWS are the two possible causes of hyponatraemia after neurosurgery. Distinguishing between the diagnosis of these conditions may be difficult as they show some overlapping clinical and biochemical signs. Extracellular volume assessment may be a key factor to distinguish between these two disorders: whereas SIADH expands extracellular volume, CSWS is characterised by extracellular sodium and fluid volume depletion. It is crucial to differentiate these two conditions since the treatment they require is different in some aspects.

SIADH

After pituitary surgery, antidiuretic hormone (ADH) secretion may occur independently of the mechanisms which normally stimulate its secretion (elevated serum osmolality and decreased intravascular volume or blood pressure). Excessive secretion of ADH, which acts upon V2 receptors located at the distal and collector tubules increasing water permeability, would cause the expansion of extracellular volume and dilutional hyponatraemia. Extracellular volume expansion is not accompanied by signs of hypervolaemia, as only one-third of the retained water is distributed through the intravascular volume. Moreover, the expansion of extracellular volume increases glomerular filtration rate and decreases sodium reabsorption at the proximal portion, thereby increasing urinary sodium excretion, which equals to that obtained through oral or intravenous intake (8).

It has been suggested that hyponatraemia associated with SIADH after pituitary surgery is caused by ADH secretion caused by axonal degeneration secondary to surgical manipulation. However, elevated ADH levels are not the rule in these patients and levels similar to those observed in normonatremic patients can be detected. As a matter of fact, the measurement of plasma ADH is not considered among the parameters requested in order to formulate a diagnosis of SIADH (9, 10).

Late hyponatraemia after transsphenoidal surgery may be due to adrenocortical insufficiency. Secondary adrenal insufficiency may be the underlying cause of a SIADH-like condition, as cortisol has proved to be a potent inhibitor of vasopressin secretion (10).

SIADH diagnosis is based on the presence of hyponatraemia together with inappropriate concentrated urine output if compared with serum osmolality, natriuresis above 20–30 mEq/l, lack of peripheral oedema or dehydration signs and absence of adrenal, thyroid or renal dysfunction. Natriuresis above 20–30 mEq/l in SIADH is explained by the increased glomerular filtration rate or by the decreased renal tubular sodium reabsorption induced by other hormones. As we have previously mentioned, when establishing a diagnosis, it is crucial to discard other causes of hyponatraemia which usually occur in patients undergoing neurosurgery (oedematous

conditions, administration of diuretics, hydric overload during the perioperative period, hypovolaemia, etc.). Moreover, the diagnosis of SIADH cannot be established when the patient undergoes severe pain, nausea, stress or hypotension, since all of these factors may stimulate ADH secretion, even in the presence of serum hypoosmolality (9, 10).

Table 2 shows the diagnostic criteria of SIADH.

CSWS

CSWS is defined by the development of excessive natriuresis occurring in patients with intracranial disease. It leads to hyponatraemia and extracellular volume depletion.

After the description of SIADH in 1957, the cases of hyponatraemia in patients undergoing neurosurgery were almost exclusively attributed to this disorder. At present, there is enough information and evidence to support the hypothesis that many of the cases of hyponatraemia occurring in the context of central nervous system disorders are caused by CSWS. Among the supporting evidence:

The negative balance of sodium precedes or accompanies the development of hyponatraemia in many patients with intracranial disease.

Many of these patients show contracted extracellular volume, which is incompatible with SIADH.

These patients show a favourable response to treatment with fluid and salt replacement instead of fluid restriction.

According to some data available, the incidence of CSWS can equal or even exceed that of SIADH in patients undergoing neurosurgery (11–13). However, in a recently published article on patients with subarachnoid haemorrhage (SAH), SIADH was the commonest cause of hyponatraemia after SAH (14).

The mechanisms by which intracranial disease leads to renal salt-wasting remain unclear, though some

hypotheses involve release of natriuretic factors (atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), C-type natriuretic peptide and ouabain-like peptide) together with decreased of sympathetic input to the kidney. These factors increase urinary sodium excretion and diminish effective arterial blood volume, which stimulates baroreceptors on ADH release. Unlike SIADH, vasopressin release in CSWS is an adequate response to volume depletion (8).

A decrease in sympathetic input to the kidney may explain the altered sodium reabsorption by the distal nephron, because the sympathetic nervous system (SNS) is involved both directly and indirectly in salt and water handling by the kidney (8). The SNS plays a key role to control renin release and a decrease of sympathetic tone leads to decreased renin and aldosterone levels despite hypovolaemia. This would explain the hyponatraemia and natriuresis observed in CSWS. Apart from the altered sympathetic input to the kidney, the release of one or more natriuretic factors contributes to sodium loss in CSWS; the ANP and the BNP contribute to the secretion of salt due to the direct inhibitory effect of salt transportation at the distal collecting tubule. Natriuretic peptides are also responsible for a decreased renin and aldosterone release. Of the above-mentioned natriuretic factors, BNP is possibly the most deeply involved in the waste of salt by the kidney (8, 15).

Differential diagnosis of SIADH and CSWS

Meticulous clinical evaluations and laboratory tests must be carried out to be able to differentiate these two disorders.

The main differential factor is extracellular volume status: hypovolaemia in CSWS and euvolaemia or hypervolaemia in SIADH (8, 15). Decreased extracellular volume with negative salt and water balance are the key diagnostic factors of CSWS which distinguish it from SIADH.

Symptoms of extracellular volume depletion include several unspecific signs such as anorexia, vomiting,

Table 2 Diagnostic criteria of syndrome of inappropriate secretion of antidiuretic hormone (SIADH)^a.

Main criteria:

1. Serum sodium < 135 mEq/l.
2. Effective decrease of extracellular fluid osmolality (serum osmolality < 275 mOsm/kg H₂O).
3. Very concentrated urine (urinary osmolality > 100 mOsm/kg H₂O with normal renal function) for any level of hypoosmolality^b.
4. Clinical signs of euvolaemia, defined as lack of signs of hypovolaemia (orthostatism, tachycardia, dry mucous membranes, decreased skin turgidity) or hypervolaemia (oedema or ascitis).
5. Elevated urinary sodium excretion (> 20 mEq/l) with normal intake of sodium and water.
6. Absence of other possible causes of euvolaemic hypoosmolality: hypothyroidism, hypocortisolism or use of diuretics.

Secondary criteria:

7. Abnormal water overload test results (inability to excrete after 4 h at least 65 or 80% 5 h after a water infusion of 20 ml/kg and/or failure to concentrate the urine (Osm urine < 100 mOsm/kg H₂O))^c.
8. Improvement of sodium levels following water restriction.

^aModified from reference 9: Verbalis JG. Management of disorder of water metabolism in patients with pituitary tumors. *Pituitary* 2002 5 119–132.

^bIt is not necessary that urine osmolality be superior to serum osmolality.

^cAlthough this test is used for the diagnosis of SIADH, it must be carefully performed and should not be carried out whenever serum sodium levels are < 124 mEq/l.

nausea, apathy and fatigue. Relevant clinical findings are hypotension, increased skin turgidity, sunken eyes, dry mucous membranes, lack of axillary sweating, tachycardia and orthostatic hypotension. In case of monitored patients with pulmonary capillary pressure or central venous pressure, a low pulmonary capillary (<8 mmHg) or central venous pressure (<6 mmHg) suggest contracted extracellular volume (7, 10, 15).

Neither the assessments of ADH serum concentrations nor the natriuretic peptides are useful to differentiate these two disorders. Elevated ADH levels can cause SIADH or they can be a consequence of extracellular volume depletion and hypoosmolality caused by CSWS (7).

Neither the severity nor the onset of hyponatraemia allows the differentiations of these two disorders, although, in CSWS, sodium concentrations are often lower as a result of excessive natriuresis. Both conditions reach their maximum peak of incidence around the seventh day after surgery.

The urinary rate flow is elevated in CSWS because of natriuresis, and is decreased in SIADH due to excessive ADH secretion (16).

It is important to take into account that in some cases hyponatraemia may be supported by a mixed condition of SIADH and CSWS (14).

Clinical and biochemical data that allow differentiation between SIADH and CSWS are shown in Table 3.

Treatment

The treatment of hyponatraemia secondary to pituitary surgery should be initiated once a differential diagnosis between CSWS and SIADH has been established. When treating a patient with hyponatraemia, it is important to bear in mind the following factors: severity and chronology of the disease, and its clinical manifestations.

In patients with serum sodium levels >120 mEq/L, hyponatraemia or its correction rarely leave after

effects, but the neurological symptoms may be significant if serum osmolality has decreased quickly. In cases of acute hyponatraemia (<48 h in duration), symptoms appear if hyponatraemia is severe (<120 mEq/l). In severe cases, there is a high risk of neurological complications and hyponatraemia should be immediately corrected. Conversely, in the case of chronic hyponatraemia (>48 h in duration), which has minimum neurological symptoms, there is a low risk of complications by hyponatraemia itself; in these cases, a rapid correction may cause serious neurological complications such as demyelination (9).

The treatment in SIADH involves fluid restriction. The restriction rate will depend on serum sodium levels. Capsulari *et al.* have suggested the following ranges according to plasma sodium levels: between 130 and 134 mEq/l, no more than 1200 ml/day, between 126 and 130, the amount of fluid is around 800 ml and it will be below 600 ml whenever natraemia is <125 mEq/l (7). Furosemide is added to the treatment when sodium concentrations are <128 mEq/l in symptomatic patients so that their sodium serum levels quickly return to normal (7). Three percent hypertonic saline solution will only be administered to patients with clinical and biochemical signs of severe hyponatraemia (serum sodium concentration <120). The infusion rate of 3% hypertonic saline solution will be established according to the level of plasma sodium and using the published formulas in each case (17; Table 4).

In cases of hyponatraemia secondary to adrenal insufficiency (SIADH-like condition), the treatment must be supplemented with hydrocortisone (9).

The treatment in CSWS involves salt and fluid replacement. Whenever sodium concentration >130 mEq/l, a specific treatment is not required. Between 125 and 130 mEq/l, sodium replacement can be done by administering physiological saline solution (0.9%) or salt in pills (1–3 g/day; (7)).

The use of hypertonic saline solution will be restricted to those situations where serum sodium concentrations

Table 3 Differential diagnosis of CSWS and SIADH^a.

Differential clinical or biochemical parameter	CSWS	SIADH
Plasma volume	↓	↑ or normal
Sodium balance	Negative	Variable
Volume depletion signs and symptoms	Present	Absent
Weight	↓	↑ or no change
Pulmonary capillary pressure	↓	↑ or normal
Central venous pressure	↓	↑ or normal
Haematocrit	↑	↓ or no change
Serum osmolality	↑ or normal	↓
Urea nitrogen/creatinine ratio	↑	Normal
Serum protein level	↑	Normal
Urinary sodium level	↑↑	↑
Urinary potassium level	↑ or no change	↓ or no change
Uric acid level	Normal	↓
Hyponatraemia during furosemide test	Persistent	Correction

CSWS, cerebral salt-wasting syndrome; SIADH, inappropriate secretion of ADH syndrome; ↓, decreased; ↑, increased; ↑↑, significant increase.
^aModified from reference 15: Harrigan MR. Cerebral salt wasting syndrome: a review. *Neurosurgery* 1996 38 152–160.

Table 4 Formula for use in managing hyponatraemia*.

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

This formula estimates the effect of 1 l of any infusate containing Na⁺ and K⁺ on serum Na⁺.

^aThe estimated total body water (in litres) is calculated as a fraction of body weight. The fraction is 0.6 in children, 0.6 and 0.5 in nonelderly men and women respectively, and 0.5 and 0.45 in elderly men and women respectively.

*Modified from Reference 17: Adrogue HJ & Madias NE. Hyponatraemia. *New England Journal of Medicine* 2000 **342** 1581–1589.

are <120 mEq/l (7). Fludrocortisone, due to its mineralocorticoid action, may be beneficial at doses of 0.1–0.4 mg/day (7, 9, 18, 19).

The rapid correction of hyponatraemia can cause pontine or extrapontine myelinolysis. The maximum correction limit is established at 1–2 mEq/l per hour and the total should not exceed 25 mEq/l during the first 48 h. Some authors suggest smaller correction limits: a maximum of 12 mEq/l during the first 24 h, 18 mEq/l during the first 48 h (9), or no more than 0.7 mEq/l per hour (7). In patients at an elevated risk of central pontine myelinolysis (i.e. patients suffering from malnutrition or alcoholism), the rate of correction should be <8 mEq/l per 24 h (20).

Discussion

Hyponatraemia after pituitary surgery can be caused by SIADH or CSWS. In the case reported, the diagnosis of CSWS was based on the following data: signs suggesting extracellular volume depletion at exploration, excessive natriuresis and an adequate biochemical response to volume replacement, oral sodium and fludrocortisone. In this case, invasive monitoring, such as measurements of central venous pressure or pulmonary capillary pressure, could not be used (a measurement of central venous pressure <6 mmHg would have provided a more accurate diagnosis). Whenever these techniques are not always available clinical examination and biochemical data together with the response to treatment can be the bases of the diagnosis with caution. In this case, our diagnosis was based on clinical and biochemical data, together with the response of the patient to the treatment.

Response to treatment can be very revealing in some circumstances. The treatment aims to reduce extracellular volume in SIADH and to replace extracellular volume and sodium deficit in CSWS. It is important to make an accurate diagnosis due to the prognostic consequences of an incorrect therapeutic management. Fluid volume restriction in CSWS worsens the existing symptoms and the use of physiological saline solution in SIADH worsens the hyponatraemia. It was not possible to perform a furosemide test in our patient, but in cases in which there is not a clear diagnosis this can be useful to differentiate between SIADH and CSWS.

The patient was treated with hypotonic solution during the first 48 h after surgery. It is known that the

use of intravenous hypotonic solutions in the postoperative period may facilitate the development of postoperative hyponatraemia (21). In this case, however, the patient developed a very high hypertonic urine with excessive natriuresis after the use of intravenous hypotonic solution in the 48 h after surgery. We believe, therefore, that the hypotonic solution did not play an important role in the occurrence of early hyponatraemia in this case. However, we cannot completely disregard the possibility that the hypotonic solution may have contributed to the development of hyponatraemia, in the light of clinical and biochemical data compatible with CSWS.

Normally, hyponatraemia occurs later after pituitary surgery, independently of being caused by SIADH or by CSWS. However, some cases of hyponatraemia have also been described during the first 24 h after surgery.

Occasionally, clinical and biochemical signs of extracellular volume depletion are not enough to distinguish between CSWS and SIADH as their clinical assessment is not very sensitive. In the absence of clear clinical signs of extracellular volume depletion or orthostatism, monitoring through the assessment of central venous or pulmonary capillary pressure makes it possible to differentiate these two disorders and to confirm the diagnosis in order to start the correct treatment.

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