

Pitfalls in SIADH-diagnosed hyponatraemia: Report of two cases

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ABSTRACT

In the majority of hospitalised patients with hyponatraemia, syndrome of inappropriate antidiuretic hormone secretion (SIADH) is the primary cause. Before considering SIADH, adrenal, thyroid and pituitary insufficiency should be ruled out. However, the evaluation of these contains potential pitfalls which could lead to incorrect diagnosing of SIADH. Here we present two cases in which a suspected SIADH turned out to be caused by hypopituitarism, emphasising the importance of correctly excluding adrenal, thyroid and pituitary insufficiency.

INTRODUCTION

Hyponatraemia, defined as a serum sodium concentration of < 135 mmol/l, is the most frequently encountered electrolyte disorder in clinical practice.^{1,2} The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is the most common underlying cause and can be suspected in euvoelaemic patients with hyponatraemia, decreased effective osmolality (< 275 mOsm/kg), high urine osmolality (> 100 mOsm/kg of water) and high urine sodium levels (> 40 mmol/l).^{2,4} SIADH should only be diagnosed after exclusion of adrenal, thyroid and pituitary insufficiency.^{2,4} However, the evaluation of these contains certain pitfalls. To emphasise the importance of correctly excluding adrenal and pituitary insufficiency, we present two cases in which a suspected SIADH was actually caused by hypopituitarism.

CASE REPORT 1

A 74-year-old male patient with no medical history was referred because of hyponatraemia. In the last three months the patient experienced progressive fatigue, weakness, weight loss and recurrent collapses. At the

What was known on this topic?

In the majority of hospitalised patients with hyponatraemia, SIADH is the primary cause. In contrast, hypopituitarism is a much rarer cause of hyponatraemia. Glucocorticoid deficiency in hypopituitarism also leads to inappropriately elevated ADH levels and mimics SIADH. Distinguishing these two clinical conditions can therefore be difficult. As a result, hypopituitarism can easily be misrecognised as a rare cause of hyponatraemia.

What does this add?

We present two cases in which hyponatraemia was caused by hypopituitarism. In both cases, SIADH was the initial diagnosis after apparent exclusion of hypocortisolism and thyroid dysfunction. These cases point out two pitfalls in the evaluation of SIADH. We emphasise the importance of thorough history taking and physical examination as these might raise the suspicion of hypopituitarism. We aim to create greater awareness for underlying endocrinological disorders in any patient with suspected SIADH.

emergency department, a hypotonic hyponatraemia of 128 mmol/l with a urine sodium level of 63 mmol/l and urine osmolality of 671 mOsm/kg were measured. Thyroid-stimulating hormone levels were within the normal range (1.9 mIU/l) after which SIADH was considered the most likely diagnosis. Further evaluation was scheduled at the outpatient clinic.

At presentation, the patient was euvoelaemic with a blood pressure of 111/75 mmHg and a pulse rate of 77 bpm. Explicit paleness was present and additional testicular examination revealed an estimated reduced volume of 10 ml. Based on these symptoms and the unexplained hyponatraemia, we suspected adrenal insufficiency. Additional testing revealed hypocortisolism

Table 1. Overview of the laboratory results on initial and secondary evaluation. The left columns illustrate the initial results on which the diagnosis of SIADH was established whereas the right columns show the additional work-up. Note that different reference values are used per case for cortisol, TSH and IGF-1 due to the use of different laboratory assays

	Case 1	Case 2	Case 1	Case 2	Reference values
Sodium	128	99	130	130	135-147 mmol/l
Potassium	4.0	3.8	4.8	4.9	3.5-5.0 mmol/l
Serum osmolality	268	209	271	272	280-300 mOsm/kg
Urine sodium	63	45	96	182	mmol/l
Urine osmolality	671	525	690	789	300-900 mOsm/kg
TSH	1.9	0.56	1.4	0.87	0.30-4.6 mIU/l
fT ₄	-		6.0	2.6	10.0-23.0 pmol/l
ACTH 08:00	-		3.3	5.3	2.2-13.2 pmol/l
Cortisol 08:00	-		76	140	125-500 nmol/l
Cortisol 13:49		360			120-620 nmol/l
Synacthen T = 0	-		-	0.15	
Synacthen T = 30	-		-	0.31	
Synacthen T = 60	-		-	0.36	
LH	-		2.7	1.6	3.0-35 U/l
FSH	-		4.3	4.4	2.0-18 IU/l
Prolactin			0.96	13	< 0.37 IU/l 59-619 mU/l
Testosterone	-		< 0.10	-	9.0-28.0 nmol/l
SHBG	-		105	-	10.0-60.0 nmol/l
IGF-1	-		8.0	0.8	6.8-23.0 8.4-26 nmol/l

TSH = thyroid-stimulating hormone; fT₄ = free thyroxine; ACTH = adrenocorticotropic hormone; LH = luteinising hormone; FSH = follicle-stimulating hormone; SHBG = sex hormone binding globulin; IGF = insulin like growth factor.

with low-normal ACTH levels, hypogonadotropic hypogonadism, central hypothyroidism and mild hyperprolactinaemia (table 1). Cranial MRI showed a 15 mm lesion in the sella turcica suggestive of a Rathke's cleft cyst. (figure 1). Based on these findings we established the diagnosis of panhypopituitarism due to a Rathke's cleft cyst. After starting replacement therapy with hydrocortisone, levothyroxine and testosterone this patient quickly made a full recovery. Ultimately, the sodium levels normalised to 140 mmol/l. A follow-up MRI scan six months later showed no growth of the Rathke's cleft cyst.

CASE REPORT 2

A 53-year-old Bolivian female patient was admitted to the intensive care unit with severe pneumonia and hypotonic hyponatraemia of 99 mmol/l. She had experienced general weakness for two weeks. Urine sodium was 45 mmol/l

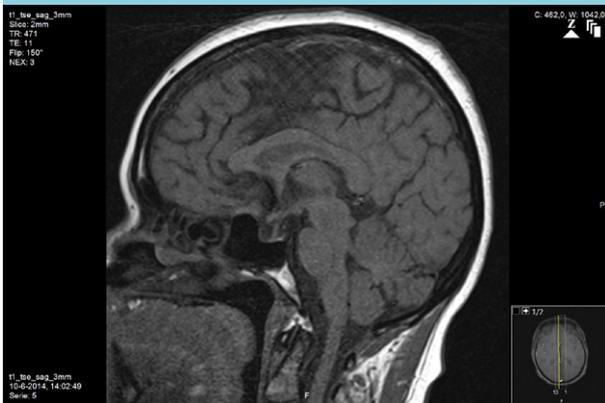
and urine osmolality was 525 mOsm/kg. Random cortisol was 360 nmol/l and thyroid-stimulating hormone was 0.56 mIU/l. Therefore, SIADH secondary to pneumonia was diagnosed and the patient was treated with antibiotics, hypertonic saline and water restriction. At discharge, she had fully recovered and her sodium level was 134 mmol/l. One week later she was readmitted with progressive abdominal pain, nausea, diarrhoea and prolonged weakness. On examination she was pale and hypotensive (BP 97/53 mmHg, pulse 72 bpm). Blood tests revealed recurrent hypotonic hyponatraemia of 130 mmol/l with a urine osmolality of 789 mOsm/kg and urine sodium of 182 mmol/l (table 1).

Based on the history, hypotension and recurrent hyponatraemia, further testing was performed. A morning cortisol level was 140 nmol/l and the ACTH stimulation test showed an insufficient response. Furthermore, central hypothyroidism and growth hormone deficiency were present (table 1). Cranial MRI showed an empty sella

Figure 1. Cranial MRI of patient A showing a 15 mm lesion in the sella turcica suggestive of a Rathke's cleft cyst. The pituitary stalk is shifted rightwards with a normal positioning of the optic chiasm. The pituitary gland is pressed towards the bottom of the sella turcica



Figure 2. Sagittal MRI of patient B showing an empty sella. There is a minimal remnant of the posterior pituitary gland visible at the bottom of the sella turcica. The pituitary stalk is slightly shifted rightwards from the midline with normal positioning of the optic chiasm



(figure 2). Additional history taking revealed that her last pregnancy in Bolivia had been complicated by heavy blood loss at delivery for which she received multiple blood transfusions. After this delivery she was unable to provide breastfeeding and she no longer had menstruation. Based on these findings we concluded a panhypopituitarism due to Sheehan's syndrome. The patient quickly recovered after starting replacement therapy with hydrocortisone and levothyroxine.

DISCUSSION

In the majority of hospitalised patients with hyponatraemia, SIADH is the primary cause.^{2,3} Underlying reasons for SIADH are diverse but can be subdivided in malignant diseases, pulmonary disorders, central nervous system disorders and the use of certain types of drugs.^{2,3} In SIADH, a physiological base (e.g. volume depletion of the extracellular fluid or hypertonicity) for the secretion of ADH is lacking, subsequently leading to inappropriately elevated ADH levels.^{3,4}

In contrast, hypopituitarism with secondary adrenal insufficiency is a much rarer cause of hyponatraemia. Space-occupying lesions, trauma or infections in the pituitary gland as well as genetic disorders involved in pituitary development can lead to corticotrophin deficiency.^{5,6} As endogenous glucocorticoids suppress both ADH and corticotrophin releasing hormone release in the hypothalamus, glucocorticoid deficiency leads to elevated ADH levels.^{7,8} These elevated ADH levels actually mimic SIADH. Hence, distinguishing these two clinical conditions might be difficult, especially in the absence of hypovolaemia or dehydration.⁸

Diederich reviewed 28 cases of severe hyponatraemia due to hypopituitarism with secondary adrenal insufficiency. Scanty/missing axillary or pubic hair (85.7%), nausea or vomiting (75%), a pale, doughy skin (71.4%) and in males a testicular volume of less than 12 ml (71.4%) were the most common clinical signs.⁹ Furthermore, anorexia, weight loss, fatigue and lack of energy or stamina are clinical signs of glucocorticoid deficiency often seen in adrenal insufficiency.⁵

The first pitfall described in our cases is the evaluation of thyroid function by measurement of solely TSH. Central hypothyroidism was present in both cases as free thyroxine levels were decreased and TSH was inappropriately normal. Even though hypothyroidism-induced hyponatraemia is rare and might only occur in severe hypothyroidism, the presence of central hypothyroidism could have pointed towards a central endocrinological problem at an earlier stage.¹⁰ Therefore, measuring solely TSH is not sufficient for excluding central endocrinological disorders in suspected SIADH.

Another pitfall is the exclusion of hypocortisolism by randomly measured cortisol levels. As serum cortisol levels are highest in the early morning, a cortisol level of < 100 nmol/l is strongly suggestive of adrenal insufficiency whereas a level of > 500 nmol/l excludes adrenal insufficiency.^{5,11} These cut-off values should be interpreted in the clinical context and are variable due to the use of different cortisol assays.¹² Case 2 illustrates that randomly measured cortisol levels are of limited use. As clinical suspicion is high and a basal cortisol level is inconclusive, dynamic testing should be performed. Both

the insulin tolerance test and the short synacthen test have been validated for diagnosing adrenal insufficiency.^{5,11,12} However, since the adrenal cortex might still be responsive in the first four weeks after onset of ACTH deficiency, the short synacthen test could be falsely normal.^{5,11,12}

CONCLUSION

Hypopituitarism with secondary adrenal insufficiency is a rare cause of hyponatraemia. It can be difficult to distinguish from SIADH, especially in the absence of hypovolaemia or dehydration. In any suspected SIADH, a morning cortisol, TSH and free thyroxine should be included in the initial work-up. If basal morning cortisol levels are inconclusive, dynamic testing of adrenal function should be performed before establishing the diagnosis SIADH.

DISCLOSURES

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REFERENCES

1. Anderson RJ, Chung HM, Kluge R, Schrier RW. Hyponatremia: a prospective analysis of its epidemiology and the pathogenetic role of vasopressin. *Ann Intern Med.* 1985;102:164-8
2. Hoorn EJ, Tuut MK, Hoorntje SJ, Van Saase JLMC, Zietse R, Geers AB. Dutch guideline for the management of electrolyte disorders-2012 revision. *Neth J Med.* 2013;71:153-65
3. Ellison DH, Berl T. The Syndrome of Inappropriate Antidiuresis. *N Engl J Med.* 2007;356:2064-72.
4. Janicic N, Verbalis JG. Evaluation and management of hypo-osmolality in hospitalized patients. *Endocrinol Metab Clin N Am.* 2003;32:459-81.
5. Charmandari E, Nicolaides NC, Chrousos GP. Adrenal insufficiency. *Lancet.* 2014;383:2152-67.
6. Crowley RK, Argese N, Tomlinson JW, Stewart PM. Central Hypoadrenalism. *J Clin Endocrinol Metab.* 2014;99:4027-36.
7. Erkut ZA, Pool C, Swaab DF. Glucocorticoids Suppress Corticotropin-Releasing Hormone and Vasopressin Expression in Human Hypothalamic Neurons. *J Clin Endocrinol Metab.* 1998;83:2066-73.
8. Oelkers W. Hyponatremia and inappropriate secretion of vasopressin (antidiuretic hormone) in patients with hypopituitarism. *N Engl J Med.* 1989;321:492-6.
9. Diederich S, Franzen NF, Bähr V, Oelkers W. Severe hyponatremia due to hypopituitarism with adrenal insufficiency: report on 28 cases. *Eur J Endocrinol.* 2003;148:609-17.
10. Liamis G, Filippatos TD, Lontos A, Elisaf MS. Hypothyroidism-associated hyponatremia: mechanisms, implications and treatment. *Eur J Endocrinol.* 2017;176:R15-R20.
11. Schneider HJ, Aimaretti G, Kreitschmann-Andermahr I, Stalla GK, Ghigo E. Hypopituitarism. *Lancet.* 2007;369:1461-70.
12. Klose M, Lange M, Rasmussen AK, et al. Factors influencing the adrenocorticotropin test: role of contemporary cortisol assays, body composition, and oral contraceptive agents. *J Clin Endocrinol Metab.* 2007;92:1326-33.