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Original Research

Hyponatremia as a leading sign of hypopituitarism

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ABSTRACT

We report the case of a 67-year-old man admitted to our hospital in an obtunded state. We found that a severe hyponatremia (115 mEq/L) was the cause of patient's status. In turn, hyponatremia was due to hypopituitarism (nonfunctioning macroadenoma). Mild to moderate hyponatremia had been previously detected in this patient, but it was overlooked. Correction of hyponatremia and treatment replacement therapy for central hypothyroidism and hypocortisolism restored a satisfactory clinical condition before discharge. The clinical onset of hypopituitarism is often characterized by mild nonspecific symptoms especially in older people, and it is often overlooked. Hypoglycemia can be another clue to undiagnosed hypopituitarism, and in the reported case, suspicious episodes of hypoglycemia occurred in the months preceding admission. Furthermore, several physicians consider hyponatremia as a normal consequence of aging. Although hyponatremia is a common electrolyte disorder in the elderly, physicians should not forget that it could be the leading manifestation of hypopituitarism. Hypopituitarism may be easily diagnosed, but clinical suspicion is needed. Because of the excess mortality associated with hypopituitarism, hormone assays should be included in the initial diagnostic work-up of hyponatremia.

1. Introduction

Hyponatremia is a common electrolyte disorder especially in the elderly [1–4], but it is also as a laboratory sign of hypopituitarism [5,6]. Hypopituitarism is a relatively rare condition that is often misdiagnosed. Hypopituitarism is an under-investigated endocrine disorder in the elderly, since its clinical features are unspecific and more often attributed to aging itself and related co-morbidities [5,6]. Thus, hypopituitarism is easily recognized when clinical suspicion is raised [5–7]. To reinforce this concept, we describe the case of a not so elderly patient whose clinical history was consistent with hypopituitarism, and highlight that the overlooked long-lasting hyponatremia could be a valuable sign driving the final endocrinological diagnosis.

Because of the burden of high mortality rate observed in patients affected from hypopituitarism [5,6], our report aim to support an adequate hormone assays in the initial diagnostic work-up of hyponatremia.

2. Background

A 67-year-old man with a seven-year history of type 2 diabetes mellitus and chronic coronary artery disease was admitted to our Division in an obtunded state. He had suffered similar episodes of depressed level of consciousness for the past eight months; during this time he appeared asthenic and remained somnolent in bed for most of the day.

He underwent surgery for a hemorrhagic duodenal ulcer and a submandibular salivary gland pleomorphic adenoma, at the age of 27 and 50, respectively. At age 60, he had an anterior myocardial infarction treated with angioplasty and stenting on the anterior interventricular artery. Five years later, he had an anteroseptal myocardial infarction complicated by a third degree atrioventricular block that was treated by implantation of a cardioverter-defibrillator.

Starting from five months prior to our admission there were two

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suspicious episodes of hypoglycemia, because symptoms disappeared upon ingesting sugar and decreasing the doses of glibenclamide.

In the last three months, he had anorexia, nausea, vomiting and a weight loss of 6 kg. Biochemical evaluations showed hyponatremia at 128 and 125 mEq/L, sixteen and four weeks prior to our observation, but it was overlooked and no further investigations were carried out.

A brain CT scan, performed while at the emergency room on the day of admission to our division, did not show abnormal findings, but the sellar region was not explored.

At admission he was unconscious and reacting only to painful stimulation with avoidance maneuvers. Skin was thin, pale, dry and cold; nails were brittle, and both axillary and pubic hairs almost absent, all these findings raising our suspicion of hypopituitarism. Pulse was 90 beats/min, respiratory rate 16 breaths/min, body temperature 36.1 °C and blood pressure 85/50 mmHg, which reinforced our suspicion of hypopituitarism. The finger stick glucose was 88 mg/dL. ECG showed a sinus rhythm and an already known left anterior fascicular block.

Blood chemistry documented severe hyponatremia (115 mEq/L) (Table 1). The promptly requested hormone assays revealed decreased serum levels of FT_4, FT_3, testosterone, LH, ACTH coexisting with borderline low serum levels of TSH, FSH and PRL; urinary and serum cortisol were low (Table 1).

A CT scan focused on the sellar region revealed a 1.5 cm pituitary oval mass with a central hypodensity; its upper portion almost reached the optic chiasm. Hence, we diagnosed anterior hypopituitarism due to a nonfunctioning pituitary macroadenoma.

Therapeutically, we started correcting hyponatremia immediately. Correction of hyponatremia was slow (1–2 mEq/L/h intravenously) because of the risk of osmotic demyelization syndrome in brain if rapid correction had occurred. On the 4th day, being aware of the said hormones results, we started replacement therapy with oral cortone acetate (25 mg/day), oral levothyroxine (75 μg/day) and intramuscular testosterone (100 mg/monthly). This therapy further improved the amelioration of the consciousness state, already seen after NaCl infusion, with disappearance of fatigue, return of appetite and increase of blood pressure (110/65 mmHg). A wellness state was reported by the patient at our last control, six months after discharge. Written consent to publish the entire patient's data has been obtained.

3. Discussion

Hyponatremia, defined as a serum sodium concentration <136 mEq/L, is a frequent electrolyte disorder in the general population [1] and in hospitalized patients [3,8]. Mild to moderate forms of hyponatremia (126–135 mEq/L) may be asymptomatic and are often overlooked. Careful history, including pharmacological history, and physical examination often provide useful clues to the underlying cause [7–10].

Thiazide diuretics and the syndrome of inappropriate ADH secretion (SIADH) are the commonest causes of hyponatremia encountered in clinical practice [7–9].

Hyponatremia could be an early sign of severe medical conditions, such as hypopituitarism [7,12]. The onset of hypopituitarism may be insidious and sometimes with mild nonspecific symptoms. Symptoms such as loss of energy, fatigue, decreased libido are common in the elderly, thus physicians often falls in misdiagnosis [5,6].

Hypopituitarism is a relatively rare disorder; its incidence and prevalence being 4.2 per 100,000 per year and 45.5 per 100,000, respectively [5]. Hypopituitarism usually develops gradually and insidiously; symptomatology is unspecific, so that diagnosis is often delayed [6,7].

Our report focuses on hypopituitarism presenting as hyponatremia (and in all likelihood also as hypoglycemia), this being the most common electrolyte disorder encountered in clinical practice [1–4,7–11]. For instance, considering a total of 5179 subjects aged 55 years or more from the population-based Rotterdam Study, Liamis et al. reported that 776 subjects (15.0%) had at least one electrolyte disorder, with hyponatremia (7.7%) and hypernatremia (3.4%) being the most common [1].

Unfortunately, several physicians consider hyponatremia, virtually a “normal” consequence of aging [6].

Our patient presented true hyponatremia, since rare causes of pseudohyponatremia (e.g. hyperproteinemia, hyperlipidemia) were simply excluded by routinary laboratory test on admission; serum osmolarity confirmed true hyponatremia (<275 mosmol/kg) and ruled out both the rarer hyperosmolar hyponatremia and pseudohyponatremia (serum osmolality ≥275 mosm/kg).

Table 1
Laboratory data.

Exams	1th day	10th day	6th month	Exams	1th day	6th month
Red blood cell count *(4-5 x10^6/μL)*	4250000	3850000	4310000	**Arterial blood gases**:		
Hemoglobin *(12–16 g/dL)*	12.3	10.9	13.2	PCO_2 *(35–45 mm/Hg)*	35.7	
Hematocrit *(%)*	37	33	39	pH *(7.35-7.45)*	7.42	
White blood cell count *(4500–9000/μL)*	5600	6200	5410	PO_2 *(80–100 mm/Hg)*	88.2	
Platelet count *(150-350 x10^3/μL)*	214000	170000	152000	SO_2 *(75–99%)*	97.3	
Creatinine *(0.5-1.4 mg/dL)*	1.1	0.9	1.1	HCO_3^- *(21–28 mEq/L)*	22.8	
Blood urea nitrogen *(10–50 mg/dL)*	72	52	49	Plasma Osmolality *(277–300 mosmol/Kg)*	277	
Electrolytes:				Urinary Osmolality *(50–1400 mosmol/K)*	395	
Sodium *(130–148 mEq/L)*	115	138	138			
Potassium *(3.5-5.2 mEq/L)*	4.6	4.7	4.3	**Hormones**:		
Calcium *(8.2-10.4 mg/dL)*	8.5	9.6	8.7	TSH *(0.27-4.2 mIU/L)*	0.33	0.31
Phosphorus *(2.5-4.6 mg/dL)*	4.2	2.9	3.2	FT_3 *(1.3-4.5 pg/mL)*	0.98	2.5
Magnesium *(1.3-2.1 mEq/L)*	1.4	1.7	1.7	FT_4 *(9.3-17.1 pg/mL)*	4	13.8
Glucose *(65–110 mg/dL)*	126	118	139	FSH *(for adult male: 1.5-12.4 mIU/mL)*	1.59	1.4
Total protein *(6-8.2 g/dL)*	5.5		6.4	LH *(for adult male: 1.7-8.6 mIU/mL)*	<0.1	<0.1
Albumin *(3-4.8 g/dL)*	3.09		3.2	Testosterone *(for adult male: 250–836 ng/dL)*	<2	310
Total cholesterol *(130–220 mg/dL)*	145		143	Urinary cortisol *(75–270 μg/24h)*	42.3	115
Triglycerides *(50–160 mg/dL)*	119		98	Serum cortisol *(5–25 μg/dL)*	5.49	14.6
AST *(0–45 U/L)*, ALT *(0–45 U/L)*	23; 9	14; 15	29; 35	ACTH *(5–50 pg/mL)*	<5	<5
γGT *(10–50 U/L)*, LDH *(150–460 U/L)*	19; 306		22; 270	Prolactin *(for adult male: 0–15 μg/L)*	2	1.1
Myoglobin *(19–92 μg/L)*	59			GH *(1–5 ng/mL)*	1.1	1.2
Troponin I *(<0.05ng/mL)*	0.02			IGF-1 *(71–290 ng/mL for male over 55 years)*	112	110

We suspected hypovolemic hyponatremia since low blood pressure and postural deficit were recorded in this patient [7].

Hyponatremia was reported to be quite common in patients with hypopituitarism. Indeed, up to 40% of patients with hyponatremia aged 65 years or older have insufficiency of the pituitary-adrenal axis [11], and hyponatremia can be the leading sign of hypopituitarism [12,13]. As well known, the same insufficiency also causes or predisposes to hypoglycemia in both diabetic and non-diabetic patients [5,6], and the patient history was suspicious for episodes of hypoglycemia even though appropriate anti-diabetic pharmacological therapy was administered [14].

Presenting symptoms are related to deficiency of anterior pituitary hormones, leading to gonadal insufficiency and hypothyroidism, and not only to adrenal insufficiency; this is true in general and also in our patient.

In addition to secondary adrenal insufficiency, hypothyroidism could contribute to the development of hyponatremia in hypopituitarism [7,9], and adequate replacement therapy is an essential step for the correction of this electrolytic disorder. However, the role of hypothyroidism is probably minimal, as hypo-osmolar status recovers as soon as cortisol deficiency is corrected, long before thyroid deficiency is adequately substituted [12,13,15]. Correcting the insufficient adrenal axis precedes correction of the insufficient thyroid axis in order to prevent adrenal crisis [16].

Hypopituitarism, and particularly hypocortisolism, may also specifically alter renal sensitivity to ADH [11].

In our patient, dynamic adrenal hormone tests and other endocrinological tests were not performed because the secondary adrenal failure was sustained by baseline assays and neuroradiology; in addition, ADH is not very accurate in low levels and not useful to confirm or exclude SIADH or diabetes insipidus (DI), and being the ACTH level undetectable, the cause of adrenal insufficiency was highly suggestive of central rather adrenal cause, thus there was no need to check aldosterone. Severe adrenal insufficiency can mask the symptoms of DI, and once steroids are replaced, some patients may need to be re-evaluated for possible DI. Furthermore, although unable to reveal causes of primary adrenal insufficiency, an abdomen echotomography showed no abnormal findings in the adrenal glands. We highlight that brain CT is not the most suitable imaging modality to investigate a suspected pituitary lesion, as suggested from the first CT scan performed in this case which missed the pituitary macroadenoma. Indeed, magnetic resonance imaging remains the gold standard instrumental test for the pituitary.

Quick and evident improvement of clinical condition occurred after correction of both hyponatremia and its underlying hormonal deficit. Hyponatremia could be an early sign of hypopituitarism, and it should not be overlooked.

Because of the excess mortality associated with hypopituitarism, hormone assays should be included in the initial diagnostic work-up of hyponatremia. Appropriate and timely therapy of hyponatremia and hypopituitarism is key to reduce the related high mortality rate.

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