PITUITARY APOPLEXY: AN OVERLOOKED CAUSE OF HYponATREMIA IN THE ELDERLY

Shwu-Jiuan Chen, Yao-Ko Wen, Yu Yang, Chia-Chu Chang

We describe a 73-year-old female patient who presented with 2-week history of general fatigue and progressive confusion, and severe hyponatremia, (serum sodium concentration of 115 mmol/L, urine sodium concentration of 73 mmol/L, and urine osmolality of 407 mosmol/kg) which was putatively attributed to syndrome of inappropriate secretion of antidiuretic hormone (SIADH). However, further investigations disclosed an etiology of hypopituitarism with secondary adrenal insufficiency and hypothyroidism responsible for the hyponatremia. Magnetic resonance imaging scan of sella demonstrated a pituitary macroadenoma with subacute hemorrhage. After hormonal replacement therapy with glucocorticoid and thyroxine, her clinical symptoms improved and the hyponatremia resolved within a few days. The patient underwent transsphenoidal resection of the pituitary adenoma uneventfully thereafter. This case illustrated that hyponatremia can be the presenting feature of pituitary apoplexy which is a frequently overlooked cause of hyponatremia in the elderly because of mimicking the laboratory diagnostic criteria of SIADH and non-specific complaints. (Acta Nephrologica 2005; 19: 135-138)

Key words: hyponatremia, hypopituitarism, pituitary apoplexy, syndrome of inappropriate secretion of antidiuretic hormone (SIADH)

INTRODUCTION

Hyponatremia is a common electrolyte disorder and often attributed to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) when the patients are normovolemic and have a normal sodium balance with urine sodium excretion rate equal to intake (urine sodium concentration usually greater than 40 mmol/L) and an inappropriately concentrated urine (urine osmolality greater than 100 mosmol/kg).1 Bacter and Schwartz, in their initial description of the SIADH, recommended that adrenal insufficiency and hypothyroidism should be ruled out because they have similar urine laboratory findings to those of SIADH.2 In primary adrenal insufficiency, hyponatremia is a classical electrolyte disorder leading to a search for adrenal failure when hyponatremia is associated with hyperkalemia and hypovolemia. However, secondary adrenal insufficiency is far more rarely sought in the patients with isolated and normovolemic hyponatremia. These patients usually complain only of nonspecific symptoms, such as fatigue, loss of energy, nausea or vomiting, or present with confusion or coma. Furthermore, many clinicians probably consider hyponatremia as a normal consequence of aging and they conduct only minimal investigations and rarely hormonal assays. These frequently lead to missing or delaying the diagnosis. Therefore, clinicians should be alert to the possibility of endocrine disturbances in elderly patients of hyponatremia with SIADH-like features. We describe herein an elderly patient of recurrent severe hyponatremia due to pituitary apoplexy with hypopituitarism which was uncovered by further hormonal studies. Although hyponatremia is not uncommon and is reported to occur in 44% of patients of pituitary apoplexy,3 to our knowledge, it rarely presents as a major problem and provides an important clue to the diagnosis of pituitary apoplexy.4-6

CASE REPORT

A 73-year-old woman presented to our emergency room with 2-week history of weakness, dizziness, nausea,
poor appetite, and general fatigue progressing to somnolence. Her past medical history was remarkable for hypertension without control. History of drug abuse or diarrhea was denied. The patient had four children and the courses of delivery were smooth without history of profuse blood loss. The menstruation was regular and her menopause occurred at the age of 52 years. On physical examination, her body temperature was 36.8°C, pulse rate 82/min, respiratory rate 16/min, and blood pressure 154/83 mmHg. The patient was normovolemic in appearance. There were no signs of jugular vein engorgement, peripheral edema, or decreased skin turgor. The patient was drowsy and disoriented. Her neck was supple and there was no focal neurological deficit. Eye movement and visual field were difficult to evaluate because of unclear consciousness. Physical examination was otherwise unremarkable except for loss of axillary hair and scarce pubic hair. Laboratory studies yielded the following results: serum sodium 115 mmol/L, potassium 3.8 mmol/L, chloride 90 mmol/L, calcium 8.8 mg/dL, blood urea nitrogen 5.2 mg/dL, creatinine 0.8 mg/dL, glucose 75 mg/dL, uric acid 4.1 mg/dL, and albumin 3.6 g/dL. Hemogram was within normal range. Chest radiograph was normal. At this time, the profound hyponatremia was considered as the sole cause responsible for her confusion and no further investigation was performed. The patient was treated with 2-liter isotonic saline infusion per day and her consciousness was regained within a few hours. She was discharged home with a serum sodium level of 123 mmol/L on the following day. Unfortunately, the patient was readmitted one week later with nausea, vomiting, and general malaise. On admission, she had normal mental status. There were no complaints of visual disturbances and visual fields were full to confrontation. Outstanding laboratory finding was a serum sodium concentration of 118 mmol/L. Urinalysis was unremarkable except for 1+ ketone. Arterial blood gas analysis was available and showed mild metabolic acidosis with pH 7.373, PCO₂ 30.6 mmHg, and total CO₂ 18.4 mmol/L. Recurrent severe hyponatremia prompted to an integrated approach to the hyponatremia. Serum osmolality was 245 mosmol/kg. Urine biochemistry revealed sodium 73 mmol/L and osmolality 407 mosmol/kg. Clinical and biochemical features strongly suggested SIADH. However, hormonal studies displayed adrenal insufficiency and hypothyroidism with morning cortisol 2.2 μg/dL (5-20 μg/dL), triiodothyronine 59 ng/dL (60-181 ng/dL), and thyroxine 5.9 μg/dL (4.5-12 μg/dL). Further hormonal assays were suggestive of hypopituitarism and showed the following results: thyroid-stimulating hormone 0.2 μU/mL (0.35-5.50 μU/mL), adrenocorticotropic hormone < 10 pg/mL (10-46 pg/mL), growth hormone (GH) 0.13 ng/mL (2.0-6.0 ng/mL), follicle-stimulating hormone 1.0 mIU/mL (1.3-11 mIU/mL), luteinizing hormone <0.5 mIU/mL (15-62 mIU/mL), and prolactin 29.0 ng/mL (1.39-24.2 ng/mL). Magnetic resonance imaging (MRI) scan of sella was performed and demonstrated a 30×25×30 mm pituitary macroadenoma with a picture consistent with subacute hemorrhage (Fig. A and B). Hormonal replacement therapy with oral prednisolone 7.5 mg/day and levothyroxine 0.1 mg/day was initiated, the hyponatremia resolved and clinical symptoms markedly improved within 2 days. Transsphenoidal resection of the pituitary tumor was performed uneventfully 2 weeks later. Pathology of the specimen showed a picture of pituitary adenoma, in which immunohistochemical stain was positive for corticotroph. After operation, the hypopituitarism was still present and the patient was put on maintenance hormonal substitution therapy. She was doing well and no more hyponatremic episodes had occurred.

**DISCUSSION**

Pituitary apoplexy is a life-threatening condition produced by destruction of pituitary tissue due to hemorrhage of infarction of the pituitary gland, most often, occurring in a preexisting pituitary tumor. In addition to a pituitary tumor, predisposing factors include anticoagulant therapy or bleeding disorders, head trauma, sudden changes in arterial or intracranial pressure, and postpartum hemorrhage. Clinical manifestations depend on extend of suprasellar compression and pituitary hormones deficiency, ranging from clinically benign events to florid neurological deficits or endocrine emergency. Partial or complete hypofunctioning of pituitary gland appears to be the rule. Veldhuis and Hammond reviewed 70 patients of pituitary apoplexy and showed hypogonadism in all patients, GH deficiency in 88%, adrenal deficiency in 66%, hypothyroidism in 42%, and diabetes insipidus in 3%. Among these endocrinopathies, gonadal dysfunction is generally neglected in the elderly and GH deficiency is usually asymptomatic in adults. Symptoms related to adrenal insufficiency or hypothyroidism are often clinically inconspicuous. Furthermore, symptoms of hypopituitarism such as fatigue and loss of energy are nonspecific and commonly considered normal in the elderly. Therefore, early recognition of pituitary apoplexy is still difficult in elderly patients despite greater than 70% of patients had laboratory evidence of hypopituitarism. Also, it is not surprising that hyponatremia at times becomes a major revealing sign in elderly patients of pituitary apoplexy without classical neurological manifestations. The indicative role of hyponatremia in elderly patients with hypopituitarism is further highlighted by the study of Diederich et
al. in which 28 patients with severe hyponatremia (mean serum sodium: \(116 \pm 7 \text{ mmol/L}\)) had been admitted to other hospitals between 1 and 4 times before being referred to the authors’ university hospital, where their hypopituitarism and secondary adrenal insufficiency were finally diagnosed.\(^{10}\) The mean age of these patients was 68 years. The most frequent signs were missing or scanty pubic and axillary hair, pale and doughy skin, and small testicles. Frequent symptoms like nausea and vomiting, confusion, somnolence or coma were similar to those in SIADH patients group.

No doubt that hypopituitarism should be thought of in all hyponatremic patients with SIADH-like clinical constellation. However, SIADH is not an uncommon disorder and hypopituitarism is much more rare than SIADH. A problem of practical relevance for clinicians is that whether an extensive hormonal evaluation is warranted in all patients presenting with SIADH. In a retrospective study of SIADH in 50 elderly patients by Hirshberg et al., only 1 of 28 patients who received a thyroid function test revealed hypothyroidism and none of 17 patients who received an adrenal function test showed abnormality.\(^{11}\) Therefore, routine diagnostic procedure using hormonal assays does not seem to be warranted in all cases. If so, another challenging issue is that under what condition hormonal study should be performed in patients with SIADH-like syndrome. A careful physical examination may be helpful in detecting the signs of endocrinopathies, while taking the history with regard to suspicious symptoms of hypopituitarism may be delayed in patients with conscious disturbance in the state of hyponatremia. In addition, a recent study demonstrated that total CO2 in patients with hyponatremia related to ACTH deficiency was significantly lower than that in SIADH (20.5 ± 3 vs. 25.5 ± 2.4 mmol/L; \(P < 0.001\)).\(^{12}\) Low plasma aldosterone levels might contribute to the result. Therefore, plasma bicarbonate level could also help to differentiate endocrine hyponatremia from classical SIADH. Finally, in the case of clinical suspicion of hypopituitarism, a basal serum cortisol level should be obtained. However, several reports suggested that normal basal values of serum cortisol might not be sufficient to exclude the possibility of adrenal insufficiency because of masking by endogenous stimulation of the hypothalamus-pituitary-adrenal axis under stress.\(^{13}\) Therefore, it is sometimes necessary to evaluate adrenal function by provocation test in severely ill patients or to reevaluate after recovery from hyponatremia. Most patients of hypopituitarism also have secondary hypothyroidism in addition to adrenal insufficiency. However, the response of hyponatremia to hydrocortisone administration is such a regular observation in most of the cases that the contribution of thyroid hormone deficiency is probably minimal.\(^{10}\) Therefore, an immediate test for thyroid function is generally not as mandatory.

Fig. (A) T2-weighted coronal magnetic resonance image scan of the sella demonstrating a 30 × 25 sellar tumor (arrow) with increased signal intensity suggestive of hemorrhage and (B) T1-weighted sagittal image also demonstrating increased signal intensity in the sellar mass (arrow) consistent with pituitary macroadenoma with subacute hemorrhage.
as adrenal function.

In conclusion, hyponatremia may be the presenting feature of pituitary apoplexy. In the clinical setting, hypopituitarism should be considered in any patient presenting with hyponatremia and SIADH-like features. Hormonal studies should be conducted when they have recurrent nature and physical signs suggestive of endocrinopathies. In suspicious cases, an assay for serum cortisol should be performed as early as possible.

REFERENCES