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Recurrent Hyponatremia as the Presenting Feature of Empty Sella

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Hyponatremia, an abnormal laboratory symptom rather than a specific disease needs the detailed search for the underlying causes. A 71-year-old female was found to have recurrent hyponatremia associated with weakness, lightheadedness and fatigue twice in the past 3 months. She had no history of psychiatric drugs administration, and previous pituitary surgery or postpartum hemorrhage. Her hyponatremia (108 mmol/L) met the laboratory diagnostic criteria of syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and was refractory to watery restriction, salt and fluid substitution alone. Endocrine studies were relatively normal including serum cortisol and thyroxine. However, provocative test with 250 μg of co-syntropin is partial response to this patient. Magnetic Resonance Imaging of brain clearly demonstrated an empty sella with cerebrospinal fluid filling in the sella turcica and flattened pituitary gland against sellar floor. Secondary adrenal insufficiency associated with empty sella was highly contributory to hyponatremia. Hyponatremia completely resolved after prednisolone supplementation. This case highlights the fact that recurrent hyponatremia mimicking SIADH may be the presenting feature of empty sella.

Key words: empty sella, hyponatremia, syndrome of inappropriate secretion of antidiuretic hormone

INTRODUCTION

Hyponatremia is the most common electrolyte abnormality in hospitalized patients on admission. It reflects an abnormal laboratory symptom rather than a specific disease and needs the detailed search for the underlying causes. To develop hyponatremia, one needs both a source of electrolyte-free water and the action of an antidiuretic hormone (ADH).[1] The reason for the high ADH action is sometimes difficult to identify in patients with euvolemic hyponatremia. In general, syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and endocrine disorders are two major differential diagnoses. Albeit indistinguishable in laboratory findings, the measurement of endocrine function helps separate these two disorders. Among endocrine disorders, glucocorticoid deficiency is the most common cause for hyponatremia which may be the foremost feature.

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The empty sella characterized by an intrasellar herniation of the suprasellar subarachnoid space within the sella turcica is often associated with some degree of flattening of the pituitary gland and can cause secondary adrenal insufficiency.[2] Adrenal insufficiency can impair water excretion and result euvolemic hyponatremia by ADH-dependent and ADH-independent mechanisms. Adrenal insufficiency is associated with elevated ADH levels, but prolonged adrenal insufficiency can also cause alternations in renal hemodynamics by an ADH-independent effect.[3] In this report, we describe a rare case with unrecognized empty sella presented with recurrent hyponatremia successfully treated with prednisolone supplementation.

CASE REPORT

A 71-year-old Chinese woman presented to an emergency department with weakness, lightheadedness, and fatigue for 3 months. In the past 3 months, she was found to have severe hyponatremia twice (Na^+ 112 and 116 mmol/L) treated with high Na diet 4000-6000 mg/day and oral NaCl 30-60 mmol/day supplement. There was no history of surreptitious diuretics or psychiatric drugs, nor was there any history of pituitary surgery or postpartum hemorrhage.

On admission, the patient's blood pressure was 160/90 mmHg, pulse rate 75 per min, and body temperature 36.5 °C.

Table 1 Biochemical studies in a patient with hyponatremia

Plasma	Normal range	D1	D14*
Hemoglobin	(12-16 g/dL)	10.5	11.0
Glucose	(70-105 mg/dL)	95	98
Osmolality	(275-295 mosm/kg.H20)	216	280
Na^+	(136-145 mmol/L)	108	138
K^+	(3.5-5.1 mmolL)	4.0	4.2
Cl^-	(98-107 mmol/L)	76	101
Urea nitrogen	(6-20 mg/dL)	10	18
Creatinine	(0.5-1 mg/ml)	0.6	0.7
Total protein	(7.1-8.7 g/dL)	8.6	–
Albumin	(4.3-5 g/dL)	4.5	–
Free thyroxine (free T4)	(0.8-2 ng/dL)	1.3	–
TSH	(0.25-5 μIU/L)	2.19	–
Cortisol	(4.3-22.4 μg/dL)	5.8	–
ACTH	(0.1-46.0 pg/ml)	15	–
Spot urine			
Na^+	(mmol/L)	89	42
K^+	(mmol/L)	22	16
Cl^-	(mmol/L)	90	28
Urea nitrogen	(mg/dL)	468	282
Creatinine	(mg/dL)	33	36
Osmolality	(mosm/kg.H_2O)	315	150

* D14, six days after prednisolone administration

She was lethargy but intact in mentality. The skin turgor and jugular venous pressure were normal, indicating normal extracellular fluid volume. She didn't have Cushing's appearance, loss of axillary and pubic hair, hyperpigmentation, and generalized myxedema. Neurological examination exhibited neither diplopia nor deficit of visual field. Blood biochemistry showed osmolality 216 mosm/kg.H_2O, Na^+ 108 mmol/L, K^+ 4.0 mmol/l, Cl^- 76 mmol/L, blood urea nitrogen 10 mg/dL, and creatinine 0.6 ng/ml. Spot urine biochemistry revealed osmolality 315 mosm/kg.H_2O, Na^+ 89 mmol/L, K^+ 22 mmol/L, Cl^- 90 mmol/L, urea nitrogen 468 mg/dL and creatinine 33 mg/dL. Endocrine studies were relatively normal (Table 1). Tumor markers, chest radiography and abdominal ultrasonography were all nonremarkable. Based on the available data, a presumptive diagnosis of SIADH was made.

Two liters of normal saline were administered per day to correct her hyponatremia initially, but the plasma Na^+ levels only reached 114 mmol/L. The restriction of water intake with previous high sodium supplement and hypertonic saline (3%) 500 ml/day have been all employed for persistent symptoms of weakness, lightheadedness, and fatigue. But plasma Na^+ levels only reached 122 mmol/L. Endocrine function was investigated again in detail, showing a normal fasting plasma growth hormone and sex hormones, but mild increase of plasma prolactin 30 ng/ml (1.8-20.3 ng/ml), low normal level of serum cortisol 5.6 μg/dL (4.3-22.4 μg/dL) and ACTH 11 pg/ml (0.1-46.0 pg/ml). Provocative test measures the serum cortisol level before and 60 minutes after an intramuscular injection of 250 μg of co-syntropin, and the serum cortisol increased to peak concentration 17.5 μg/dL, revealing partial response to co-syntropin.

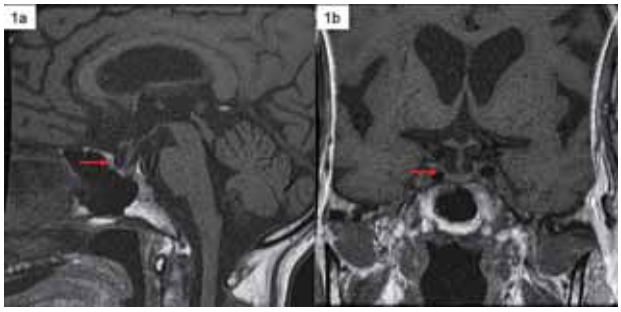

Fig. 1 Sagittal(1a) and coronal(1b) T1-weighted MRI of pituitary demonstrate an apparent empty sella with cerebrospinal fluid filling in the sella turcica, pituitary stalk remaining in the midline, and the pituitary gland flattened against sellar floor.

Magnetic Resonance Imaging (MRI) of the brain clearly demonstrated an apparent empty sella with cerebrospinal fluid filling in the sella turcica, pituitary stalk remaining in the midline, and the pituitary gland flattened against sellar floor (Figure 1). Secondary adrenal insufficiency associated with empty sella was highly contributory to hyponatremia. Her hyponatremia and associated symptoms completely resolved within 6 days after oral prednisolone replacement (10 mg/day) alone, without salt supplementation and water restriction (Table 1). With the treatment of daily supplement of prednisolone 7.5 mg, it was maintained in the 135-140 mmol/L range without Na^+ supplement or water restriction during the 6 months' follow-up.

DISCUSSION

In this patient with recurrent euvolemic hyponatremia had a high urine Na^+ concentration, and an inappropriate urine osmolality suggestive of inappropriate ADH action. Physical findings in patients with adrenal insufficiency are subtle and nonspecific. In the setting of acute stress, such as the exacerbated dizziness and fatigue of our patient, an increase in cortisol production may let adrenal

insufficiency to be presented with a "normal" cortisol concentration. Morning serum cortisol below 3μg/dL is virtually diagnostic for adrenal insufficiency, whereas cortisol values comprised between 4.3-22.4 μg/dL have limited sensitivity and require additional investigations.[4] In this patient, low-normal level of cortisol and ACTH, and parital respond to co-syntropin confirm the presence of secondary adrenal insufficiency. Any process that involves the pituitary and interferes with ACTH secretion can cause secondary adrenal insufficiency. The pituitary MRI can help us to search for underline structure abnormalities of pituitary inducing secondary adrenal insufficiency.

The etiology of empty sella can be secondary or primary. Secondary empty sella may be caused by pituitary adenomas with spontaneous necrosis, infection, autoimmune, trauma, radiotherapy, drugs, and surgery.[5] Primary empty sella is definited associated with congenital incomplete formation of the sella diaphragm and intermittent increase in intracranial pressure as well as volumetric changes in the pituitary gland. The most frequent cause of the endocrinological dysfunction is the primary pituitary dysfunction.[6]

Most primary empty sella patients are asymptomatic with normal pituitary function.[7,8] Some patients with empty sella may have panhypopituitarism or partial hypopituitarism. The cause of hypopituitarism has not been well-defined. Pituitary stalk compression has been considered as a consequence of remodeling of the hypothalamo-pituitary region and altered CSF dynamics, which frequently caused mild hyperprolactinemia (accounted for 10% of primary empty sella patients).[5] It has been hypothesized that a furthermore compression of pituitary gland due to a progressive hypotrophy or an increase in intrasellar pressure results in these heterogeneous endocrine conditions, ranging from global or partial hypopituitarism to various isolated pituitary hormones dysfunction, include isolated adrenocorticotropin deficiency. Partial hypopituitarism has been described in 5 % of patients.[9,10] Therefore the initial presentation of empty sella depends on heterogeneous endocrine function.

Hyponatremia can be a severe complication of hypopituitarism in empty sella syndrome.[11] Diederich et al. reported that 20 % of patient with severe normovolemic hyponatremia were suffering from previously unrecognized hypopituitarism and secondary adrenal insufficiency, most due to empty sella (43%), Sheehan's syndrome.[12] and pituitary tumor.[13] Most of them were women. Severe hyponatremia caused by hypopituitarism in the elderly is frequently overlooked. Most of them suffer from non-specific symptoms and signs during the preceding years before diagnosis, and frequently were misdiagnosed to SIADH without appropriate treatment.

Hyponatremia can result from the defect in water excretion in glucocorticoid insufficiency. The impaired water excretion associated with glucocorticoid deficiency is mediated by both ADH-dependent and ADH-independent mechanisms. In ADH-dependent mechanism, extracellular fluid volume depletion associated with glucocorticoid deficiency stimulates nonosmotic relase of ADH and impair renal hemodynamics. The ADH-independent mechanism is a decrease in distal fluid delivery associated with a significant decrease in cardiac output and renal blood flow caused by glucocorticoid insufficiency.[14,15] Once secondary adrenal insufficiency is diagnosed, hyponatremia could be rapidly corrected by hydrocortisone replacement (15 to 25 mg of hydrocortisone).[16] Glucocorticoid substitution in combination with concurrent saline infusion and restriction of electrolyte-free water intake in treating empty sella syndrome may develop osmotic demyelination syndrome.[17] Clinicians should frequently monitor serum sodium level and neurologic signs during the treatment.

In conclusion, we describe a rare case with recurrent hyponatremia due to empty sella with secondary adrenal deficiency mimicking SIADH. Our case highlights the fact that normal serum cortisol concentration can not exclude the possibility of adrenal insufficiency without the provocative test and searching for the underlyng cause of this treatable or curable disorder can avoid inappropriate therapy

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