SIADH Closely Associated with Non-functioning Pituitary Adenoma

Masaaru Kanda, Yoshio Omori, Soji Shinoda, Tomohiko Yamauchi*, Hirohiko Tamemoto*, Masanobu Kawakami* and San-e Ishikawa

Department of Surgical Neurology, Jichi Medical School, Omiya Medical Center, Saitama 330-8503, Japan
*Department of Medicine, Jichi Medical School, Omiya Medical Center, Saitama 330-8503, Japan

Abstract. We demonstrated severe hyponatremia in a 68 year-old man who had pituitary tumor. He had poor appetite and was disoriented. Tests revealed hyponatremia of 110 mmol/l, and he was admitted to Jichi Medical School Omiya Medical Center to undergo further tests. Physical findings revealed disturbance of consciousness with Japan Coma Scale I-2. There was neither dehydration nor edema. Laboratory data showed a serum sodium level of 112 mmol/l; plasma osmolality, 219 mmol/kg; and urinary osmolality, 555 mmol/kg. Plasma arginine vasopressin (AVP) level was 1.6 pmol/l despite the marked hypoosmolality. Anterior pituitary function was normal. Brain magnetic resonance imaging showed a pituitary tumor of 20 × 18 × 20 mm in size, which pushed the pituitary stalk upward. After the adenomectomy, serum sodium level was kept normal without any treatment. Histology showed basophilic adenoma. These findings indicate that local pituitary tumor may cause exaggerated secretion of AVP, resulting in the syndrome of inappropriate secretion of antidiuretic hormone (SIADH).

Key words: SIADH, Arginine vasopressin (AVP), Pituitary gland, Hyponatremia


HYponATREMIA is the hallmark of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) [1], and belongs to the category of euvolemic hyponatremia [2]. Inappropriate secretion of arginine vasopressin (AVP) is classified into two groups: ectopic production of AVP, and release from posterior pituitary gland closely related to disorders of the central nervous system, pulmonary disorders and drug administration [3]. Ectopic AVP-producing tumor is evident if AVP is found in cancer tissue by immunocytochemistry. In contrast, the mechanism of AVP release from the posterior pituitary is not clear in disorders of the central nervous system. There is no evidence for stimulatory factors or afferent pathways to the posterior pituitary.

Pituitary tumor can be related to hyponatremia. If so, secondary hypopituitarism, particularly dysfunction of the pituitary-adrenal axis, should exist, and such hyponatremia is independent of SIADH [4, 5]. However, there are a few reports that SIADH occurs in patients with pituitary tumor whose pituitary function is normal [6–8]. The exaggerated release of AVP could be due to local mechanical stress. The present study was undertaken to evaluate the relation of hyponatremia to pituitary tumor, and to elucidate the possible mechanism of non-suppressible release of AVP.

Case Report

A 68 year-old man had poor appetite for the last several days, and then gradually became disoriented. Since the symptoms worsened, he visited a physician. Severe hyponatremia of 110 mmol/l was uncovered, and he was admitted to our hospital to undergo further examinations for the pathogenesis of hyponatremia in May 2002. Physical findings were: height, 161 cm; body weight, 60.9 kg; blood pressure, 120/64 mmHg.
without postural change; and pulse rate, 72 beats/min with regular rhythm. His consciousness had deteriorated to class I-2 on Japan Coma Scale. He was not thirsty, and had neither dry skin or tongue, nor pretibial edema. Neurological examination showed no abnormal findings. Laboratory findings showed white blood cells were 4290/cmm; red blood cells, $347 \times 10^4$/cmm; hemoglobin, 109 g/l; hematocrit, 30.4%; and platelets, $31.1 \times 10^4$/cmm. Serum sodium (Na) level was 112 mmol/l; potassium, 4.9 mmol/l; and chloride, 78 mmol/l. Blood urea nitrogen was 15 mg/dl; serum creatinine 115.4 μmol/l; and serum uric acid, 232 μmol/l. Plasma osmolality (Posm) was 219 mmol/kg and urinary osmolality (Uosm), 555 mmol/kg. Urine volume ranged from 900 to 1600 ml/day. Plasma AVP level was 1.6 pmol/l despite the marked hypotonicity. An acute oral water load test was done on the 25th hospitalized day when serum Na level was 136 mmol/l, and indicating impaired water excretion, as the percent excretion of water loaded was only 16.1% and minimal Uosm was 613 mmol/kg. Plasma ACTH level was 5.3 pmol/l, with serum cortisol of 253.8 nmol/l. Serum LH and FSH were 1.6 and 3.4 IU/L; serum GH, 0.65 μg/l; serum TSH, 1.52 mU/l; and serum prolactin, 15.0 μg/l. Brain magnetic resonance imaging (MRI) showed a pituitary tumor with a size of $20 \times 18 \times 20$ mm, which pushed the pituitary stalk upward (Fig. 1).

Hyponatremia was controlled by water intake restriction (15 ml/kg body weight per day) and administration of furosemide 20 mg per day. Serum Na levels increased to 135 mmol/l before the operation. The pituitary tumor was removed by transsphenoidal adenomectomy. The histological finding showed basophilic adenoma. After the operation, serum Na levels further increased to 139 mmol/l, and remained at normal level without water intake restriction and any medication (Fig. 2). There was no occurrence of postoperative diabetes insipidus in the patient. Hematocrit increased from 30.1 to 33.1% according to the normalization of serum Na levels. The change in hematocrit could indicate an alteration in circulatory blood volume, which showed an 8.4% increase in the hypotonic state compared with that in the steady state.

![Fig. 1. T1-weighted MR image of the brain. (A) Plain MRI. Coronal projection, (B) Plain MRI. Sagittal projection, (C) Gadolinium enhancement. Coronal projection, and (D) Gadolinium enhancement. Sagittal projection. The pituitary tumor compressed the pituitary stalk (arrow) upward.](image-url)
Acute water load test was carried out again, and the percent excretion of water loaded was 38%, minimal Uosm was 228 mmol/kg, and minimal plasma AVP was 0.7 pmol/l. Hyponatremia has not recurred in the 14-month postoperative period. In addition, postoperative MRI showed that the compression of the stalk was released (Fig. 3).

**Discussion**

The clinical and laboratory features were consistent with the diagnostic criteria of SIADH by Bartter and Schwartz [1]. There were hyponatremia, hypoosmolality, hypertonic urine, neither dehydration nor edema, and normal renal and adrenal function. Though the pituitary tumor occupied the sella turcica, the function of the pituitary gland remained normal. As noted earlier, both plasma ACTH and serum cortisol levels were in the normal range. Hyponatremia was closely related to the impairment in renal water excretion dependent upon the nonsuppressible release of AVP [2, 3]. Plasma AVP level of 1.6 pmol/l was relatively high compared to the Posm of 219 mmol/kg, and its value was in the normal range. Also, serum Na level was kept normal without any treatment after the operation, and recurrent hyponatremia has not occurred. These find-
ings do not suggest the possibility of ectopic AVP production in the present patient.

Regarding the pathogenesis of increased AVP secretion in the present patient, it is important to evaluate anatomical interaction between the pituitary tumor and hypothalamo-neurohypophysial system. As shown in Fig. 1, the pituitary tumor occupied the sella turcica and pushed the pituitary stalk upward. After the operation, the compression was improved as shown in Fig. 3. The dislocation of the pituitary gland resulted in an inappropriate secretion of AVP. This possibility was strongly suggested by the observation of prompt disappearance of hyponatremia after the adenomectomy. Also, as noted above, the plasma level of AVP was not so high as that in patients with ectopic AVP production. As local, non-specific mechanical stress may cause the inappropriate secretion of AVP, the pituitary tumor may account for one of the causes of SIADH. This is possible a rare disorder, as only four such cases have ever been reported in the literature [6–8].

Disorders of central nervous system cause SIADH, in which AVP is released from posterior pituitary gland. They include meningitis, encephalitis, cerebrovascular events, subarachnoid hemorrhage, subdural hematoma, brain tumor and so on [2, 3]. However, it is unclear how such disorders produce inappropriate secretion of AVP in these pathological states. Either mechanical or chemical stimulation could be suspected to affect the hypothalamo-neurohypophysial system. In this point of view, mechanical stress is highly likely to be involved in non-suppressible release of AVP in the present patient. The present study is of value to develop the evaluation for the mechanism of inappropriate secretion of AVP in SIADH related to the disorders of the central nervous system.

In conclusion, we demonstrated severe hyponatremia in a patient with non-functioning pituitary tumor. The pituitary tumor exerted mechanical stress that pushed the pituitary stalk upward, producing inappropriate secretion of AVP.

References