J Korean Med Sci 2001; 16: 677-82
ISSN 1011-8934

Hypodipsic Hypernatremia with Intact AVP Response to Non-Osmotic Stimuli Induced by Hypothalamic Tumor
: A Case Report

Anatomical lesions of hypothalamic area associated with hypodipsic hypernatremia have been reported only rarely. We report here a case of hypodipsic hypernatremia induced by a hypothalamic lesion. A 25-yr-old man, who had been treated with radiation for hypothalamic tumor 5-yr before, was admitted for evaluation of hypernatremia and hypokalemia. He never felt thirst despite the elevated plasma osmolality and usually refused to drink intentionally. Plasma arginine vasopressin (AVP) level was normal despite the severe hypernatremic hyperosmolar state and urine was not properly concentrated, while AVP secretion was rapidly induced by water deprivation and urine osmolality also progressively increased to the near maximum concentration range. All of these findings were consistent with an isolated defect in osmoregulation of thirst, which was considered as the cause of chronic hypernatremia in the patient without an absolute deficiency in AVP secretion. Hypokalemia could be induced by activation of the renin-angiotensin-aldosterone system as a result of volume depletion. However, inappropriately low values of plasma aldosterone levels despite high plasma renin activity could not induce symptomatic hypokalemia and metabolic alkalosis. The relatively low serum aldosterone levels compared with high plasma renin activity might result from hypernatremia. Hypernatremia and hypokalemia were gradually corrected by intentional water intake only.

Key Words : *Hypodipsia; Hypernatremia; Argipressin; Hypothalamic Neoplasms*

Mi-Ja Kang, Kun-Ho Yoon, Seong-Su Lee, Jung-Min Lee, You-Bae Ahn, Sang-Ah Chang, Moo-Il Kang, Bong-Yun Cha, Kwang-Woo Lee, Ho-Young Son, Sung-Koo Kang, Yong-Kil Hong*

Departments of Internal Medicine, and Neurosurgery*, Catholic University of Korea College of Medicine, Seoul, Korea

Received : 24 July 2000
Accepted : 26 December 2000

Address for correspondence
Sung-Koo Kang, M.D.
The Division of Endocrinology, Department of Internal Medicine, Catholic University Medical Center, Holy Family Hospital, 2 Sosa-dong, Woonmi-gu, Puchun 422-717, Korea
Tel : +82.32-340-2257, Fax : +82.32-320-2667
E-mail : skkang@hfh.cuk.ac.kr

INTRODUCTION

The levels of plasma osmolality and sodium ion are maintained by regulation of hypothalamic osmoreceptor, which controls water intake and vasopressin release. Temporal hypernatremia after hypothalamic surgery or trauma can be observed with various degrees of anti-diuretic hormone (ADH) deficiency. However, persistent hypodipsia and hypernatremia associated with anatomical lesions in the hypothalamic area is an uncommon syndrome. Although there have been additional reports (1-18) since Schaad et al. (19) described patients with "hypodipsia-hypernatremia" in 1979, this is the first case report in Korea. Abnormal ADH secretion was demonstrated in some cases of hypodipsic hypernatremia. Some showed normally regulated ADH secretion by serum osmolality but others have shown the ADH secretion was dependent on non-osmotic, almost hemodynamic stimuli only. We report a case of chronic hypodipsic hypernatremia with an intact ADH response to non-osmotic stimuli induced by hypothalamic lesions such as hypothalamic tumor.

CASE REPORT

A 25-yr-old man was admitted for evaluation of asymptomatic hypernatremia. Five years prior to admission, a brain tumor was found in his thalamus (Fig. 1). It was treated with 2200 cGy radiation for 2 weeks without prior pathologic confirmation. After discharge, the brain tumor was followed up with brain MRI on a neurosurgical out-patient basis, which demonstrated a complete regression of the tumor. Since the development of the disease, hypernatremia, hyperosmolality, and hypokalemia were sustained but a proper evaluation was not performed. He never felt thirsty despite the elevated plasma osmolality and did not drink spontaneously. He usually refused fluids when they were offered. Physical and neurological examinations showed blood pressure at 100/60 mmHg, pulse 76/min, body temperature 37.2℃, weight 86 kg, height 175 cm, and a non-dehydrated tongue with normal skin turgor. Mental status was alert and mental function was partially preserved; he showed intact orientation but had impaired memory and defect in retention, calculation, and judgement. Mild right

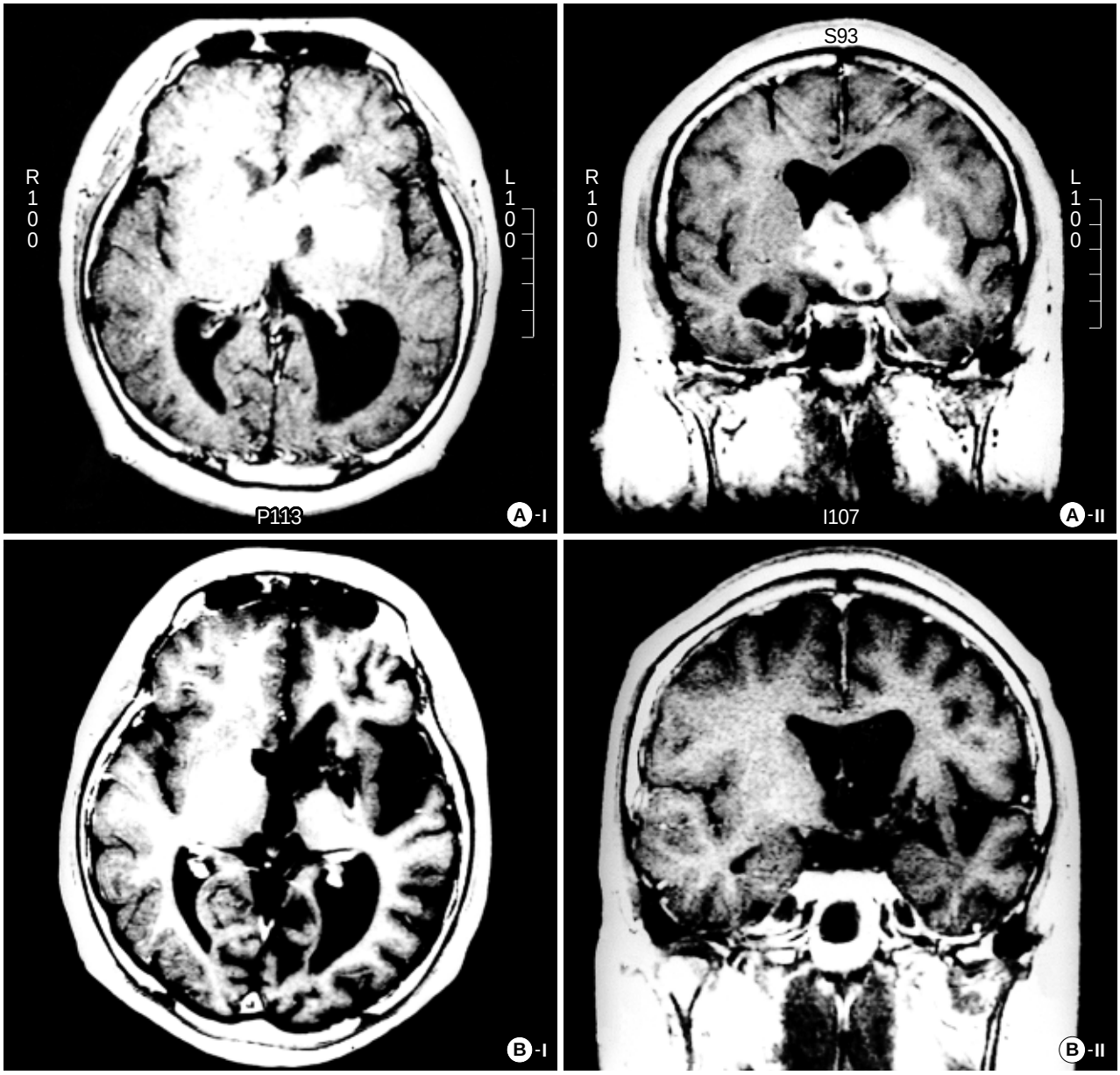

Fig. 1. Brain MRI (A) at admission (1995.11.1). There is a large contrast-enhanced mass involving the optic chiasm, hypothalamus, thalami on the left side, and region of the foramen Monroe with extention to the septum pellucidum and anterior horns. (B) Follow-up MRI (1999.10.24) shows a complete resolution of the previously noted mass in the region of the left basal ganglia.

side motor weakness was also observed. Laboratory data included a hemoglobin value of 11.9 g/dL, hematocrit 35.3%, serum creatinine 1.23 mg/dL, uric acid 10.7 mg/dL, BUN 16.6 mg/dL, glucose 102 mg/dL, Na^+ 168 mEq/L, K^+ 3.1 mEq/L, Cl^- 121 mEq/L, total protein 5.9 g/dL, albumin 3.7 g/dL, osmolality 346 mosm/kg, urine specific gravity 1.020, urinary Na^+ 132 mEq/L, K^+ 36 mEq/L, osmolality 623 mosm/kg, and TTKG (transtubular K^+concentration gradient) 6.4. Thyroid function test was T_3 0.72 ng/mL (normal 0.78 to 1.82), T_4 3.12 μg/dL (normal 4.68 to 12.48), TSH 2.3 μIU/mL (normal 0.17 to 4.05), and Free T_4 0.44 ng/dL (normal, 0.85 to 1.86). Growth hormone (GH) was 0.26 ng/mL (normal, 0.85 to 1.86), prolactin 13.69 ng/mL (normal, 2 to 15), adrenocorticotropic hormone (ACTH) 35.06 pg/mL (normal, 9 to 52), cortisol 2.74 μg/dL (normal, 5 to 25), and testosterone 1.6 ng/mL (normal, 3 to 10). On the fourth day of admission, a combined pituitary stimulation test was performed. We could predict that hypo-thalamic abnormalities were responsible for low end hormone levels (Table 1). After diagnosis of hypothalamic dysfunction by combined pituitary function test, glucocorticoid and thyroid hormone replacement was started. Hormone replace-

Table 1. Combined pituitary stimulation test

Time	GH (ng/mL)	ACTH (pg/mL)	Cortisol (μg/dL)	Glucose (mg/dL)	TSH (μIU/mL)	T_3 (ng/mL)	free T_4 (ng/dL)	Prolactin (ng/mL)	LH/FSH (mIU/mL)	Testosterone (ng/mL)
Basal	0.33	51.77	4.96	71	1.65	0.72	0.44	21.22	2.93/3.41	1.6
30 min	0.89	66.68	10.47	40	19.68			41.05	43.6/10.3	
45 min	0.78	66.69	10.70	105	16.94			37.8	41.8/11.0	

A combined pituitary stimulation test was done. We could see that hypothalamic stimulation abnormality was responsible for the low end hormone level and diagnosed him as tertiary hypothyroidism, tertiary hypogonadism, and tertiary adrenal insufficiency. If he was stimulated with CRH and GRH, the ACTH and GH levels could be elevated. However, primary GH deficiency could not be completely excluded.

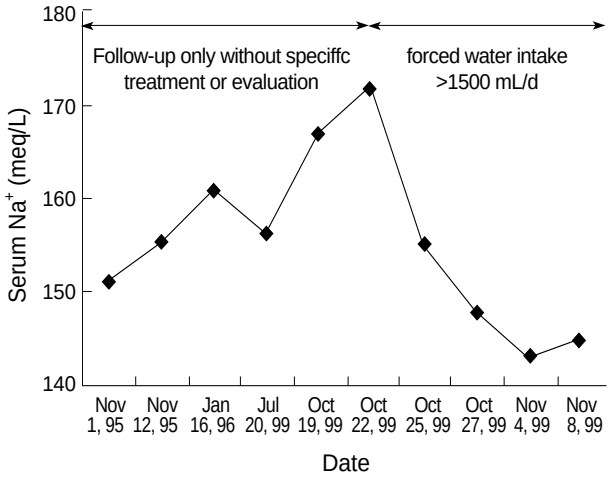

Fig. 2. The change in serum Na^+ level with the amount of water intake. After daily intake of 2.0 L of water, a change in plasma Na^+ values was observed. Progressive normalization of hypernatermia was observed.

ment did not influence the concentrations of serum electrolytes. We strongly recommended drinking 1.5 L of water daily. Intentional water intake could elicit the gradual normalization of hypernatremia (Fig. 2).

A water deprivation test was performed on 10th day of admittance (Table 2). Water deprivation began the night preceding the test; the patient did not eat anything for 9 hr before the test. We obtained hourly blood and urine for serum osmolality, serum sodium, urine osmolality, urine specific gavity, and urine sodium for 9 hr. Hourly measurements of body weight, urine volume, and plasma ADH were made, also. Before the test, plasma ADH level was within the normal range despite the hypernatremic (155 mEq/L) hyperosmolality. No vasopressin was administered. However, plasma ADH level was rapidly elevated during water deprivation. Together with the increasing plasma ADH level, urine osmolality also gradually increased over time.

Evaluation for potassium ion showed that hypokalemia developed simultaneously with hypernatremia (Table 3). With hypokalemia, a very high plasma renin activity and only slightly elevated serum aldosterone levels were observed.

Since his disgnosis of brain tumor in 1995, the patient had complained of intermittent fever of non-infectious origin. Under the diagnosis of fever originated from hypothalamic dysfunction, propranolol was administered up to 30 mg every 6 hr (20). However, fever was not controlled to normal range for 5 days, and we stopped administering propranolol. He was dischaged on the 26th hospital day with prescription of a steroid and thyroid hormone replacement, and was recommended to drink 1.5 L of water per day.

DISCUSSION

Water balance and osmolality are controlled via hypothalamic integration of signals from osmoreceptors and neurosecretary response with output of vasopressin to various stimuli. In the maintenance of normal plasma osmolality,

Table 2. Water restriction test and serum ADH level

	At adm. 19/10/99	Water drinking 25/10/99	Over night fasting start 28/10/99	Dehydration for 6 hrs	Dehydration for 9 hrs	Dehydration for 12 hrs	Dehydration for 15 hrs
Serum sodium (mEq/L)	168	155	147	145	144	146	145
Serum osmolality (mOsm/kg)	346	308	292	302	304	294	296
Urine osmolality (mOsm/kg)	623	505	734	702	761	1760	1586
Urine sodium (mEq/L)	132	171	150	91	29	60	45
Urine volume (mL/hr)	700/day	2700/day	50 mL/hr	45 mL/hr	50 mL/hr	20 mL/hr	20 mL/hr
Plasma AVP (nL:1.0-6.7 pg/mL)		1.32		>14.16	>14.16	>14.16	>14.16

His weight decreased from 81.25 to 79.65 kg (1.98 percent). Contrasting with the data of preceding water deprivation test, serum osmolality and sodium levels show remarkable changes. Plasma ADH and urine osmolality increased according to the severity of dehydration. Intact ADH secretion and ability of urine concentration are observed. We could rule out diabetes insipidus.

Table 3. Changes in serum electrolytes, renin and aldosterone levels

	Oct.22	Oct.25	Oct.27	Nov.5	Nov.6	Nov.8	Nov.11	Nov.13
Serum K (mEq/L)	2.78	3.7	3.9	3.7	3.8	3.4	3.4	3.4
Serum Na (mEq/L)	172	155	148	155	149	145	147	149
TTKG	6.2	7.7	9.7	7.1	6.3			
PRA (ng/mL/hr) basal/stimulated			3.99	8.05/14.93			7.39	
Aldosterone (pg/mL) basal/stimulated			47.15	103.88/274.04			33.85	

Hypokalemia might be due to the activation of renin-angiotensin-aldosterone system (TTKG>4). We can observe parallel fluctuation of serum sodium and aldosterone concentrations during the follow-up period. These findings suggest that hypernateremia could play a permissive role in aldosterone secretion, which is the normal response to renin. Samples for PRA and plasma aldosterone are obtained after supine position for 30 min and uplight posture for 4 hr.

even a small increase in plasma osmolality triggers two physiologic mechanisms: stimulation of thirst accompanied by consequent water intake and ADH secretion which increases renal water reabsorption (1). Patients with decreased mentality may become volume-depleted due to the lack of replacement of insensible water losses. This sequence may produce hypernatremia because water is lost in proportion to the excess of sodium (21). However, severe hypernatremia is not induced if osmoreceptors that respond to hyperosmolality are intact. Anatomical lesions of the hypothalamic area associated with hypodipsic hypernateremia have been reported only rarely. Hypothalamic dysfunction has been described most often as it is usually due to tumors, especially germinoma, glioma, granulomatous diseases such as sarcoidosis, and vascular diseases (22, 23).

In this case, the derangement of osmoregulation was induced by a hypothalamic tumor; and radiotherapy of the tumor resulted in hypodipsia despite the hypernatremia and hyperosmolality. Water deprivation could elicit an intact AVP release and normal renal response to AVP (Table 2). On the basis of these data, we could make a diagnosis of hypodipsic hypernatremia with intact AVP response to non-osmotic stimuli induced by a hypothalamic tumor. We deduced that hypernatremia in this patient developed as follows: 1) hypodipsia reduced the patient to a mildly dehydrated state; 2) the mild hypovolemic state induced sodium reabsorption by activating the renin-angiotensin-aldosterone system; and 3) finally hypernatremia, hypokalemia and euvolemia were sequentially induced. Due to the destruction of the hypothal-mic osmoreceptor, the AVP secretion response to hypernatremia and hyperosmolality was blunted and hypernatremia progressed. With hypokalemia, a very high plasma renin activity and only slightly elevated serum aldosterone levels were observed. The hypokalemia could be due to the activation of renin-angiotensin-aldosterone system reflected by high transtubular potassium gradient (TTKG>4). We could observe parallel fluctuations of the serum sodium and aldosterone concentrations during the follow-up period (Table 3). These findings suggest that hypernatremia might play a permissive role in aldosterone secretion (24, 25). Hypokalemia also appears to contribute to the hypoaldosteronism (12, 26). A reduction in plasma aldosterone was observed by Crozier et al. (1986) following intravenous infusion of atrial natriuretic peptide (ANP) wherein the plasma atrial natriuretic peptide (ANP) level was raised to 191 pg/mL. In the present case, the plasma ANP concentration was 14 pg/mL (normal, <40) and the ANP-mediated suppression of aldosterone secretion appears un-likely. However, normal level of serum ANP despite severe hypernatremia in the absence of dehydration may suggest altered ANP regulation in this patient. This chronic euvolemia and mild hypovolemia can not stimulate ADH secretion. However, acute dehydration induced AVP secretion and maintained normonatremic normoosmolality. Deficiency of AVP secretion was demonstrated in well-documented cases of hypernatremia, while a hypernatremic syndrome with absence of thirst, normal, osmotically regulated vasopressin secretion, and abnormalities of central nervous system was recently observed (28).

Fabris et al. described that their patient falled on the middle of the spectrum of hypodipsic hypernatremic syndrome, that is, between the majority of patients with little or no osmotically mediated AVP release and the recently described case of a child, who had a completely normal AVP secretion (1). It is well known that vasopressin secretion may not be influenced by osmotic stimulation in hypothalamic anatomical derangement.

According to Robertson et al., osmoreceptors are relatively insensitive, rather than being reset at a higher level. The appropriate response in this setting may be mediated by the volume receptor function (22). The essential hypernatremia represents a selective damage to the osmoreceptors resulting in hypodipsia, hypernatremia, and volume-mediated AVP release. This hypothesis has been confirmed in at least one patient whose plasma ADH levels increased normally with correction of hypotension, but changed little with an elevation in plasma osmolality (27).

Our case shows that the dissociation of hypodipsia from hy-povasopressinemia indicates the neuronal pathways that mediate osmoregulation of thirst and vasopressin secretion in humans are sufficiently discrete to be affected selectively. Whether this anatomical separation begins at the level of the osmoreceptors themselves or occurs further on in the efferent pathway is unknown. However, the functional dis-

sociation does indicate that defects in one osmoregulatory system need not be accompanied by an abnormality in the other (28).

In hypodipsic hypernatremia, the symptoms of chronic hypernatremia itself may be absent. However, the underlying neurologic disease frequently precedes the onset of hypernatremia, and it may be difficult to tell initially whether the neurologic abnormalities are in fact due to the increase in plasma Na^+ concentration. For example, patients with hypodipsia and essential hypernatremia have hypothalamic lesions which may be due to tumors. In the diagnosis of hypodipsic hypernatremia, the most important point is that there is no spontaneous drinking despite hyperosmolar state. Other helpful diagnostic tests, although not confirmed, are water restriction test and hypertonic saline infusion test. Up to present, there has been no confirmatory diagnostic test.

The proper treatment for patients with hypothalamic dysfunction with normal AVP secretion can be simply forcing the patient to drink water. Patient can be instructed to drink 1,500 to 2,000 mL of water per day, regardless of thirst. Correction of hypernatremia is somewhat more difficult in hypodipsic patients with completely impaired AVP secretion. In these conditions, a water loading only induces polyuria, and hypernartremia will be sustained. Chloropropamide, which enhances the action of the small amount of AVP being released, has proven to be effective in these patients. However, there is some risk of hyponatremia, since the osmoreceptor defect may prevent complete suppression of AVP release after a water load (22).

Dunger et al. presented the first direct evidence for increased renal sensitivity to exogenous AVP in patients with essential hypernatremia. DDAVP administered to the patients for 3 months showed a return of this response toward normal, and they also reported that treatment with DDAVP led to a sensation of thirst (13). In this case, we did not try DDAVP to rekindle the sense of thirst because hypernatremia was well controlled with intentional water intake only and the use of DDAVP might have led to hyponatremia.

We report a case of hypodipsic hypernatremia induced by selective defects of AVP secretory response to hyperosmolality due to brain tumor. In this patient, AVP response to nonosmotic stimuli was well preserved but hypothalamic hypopituitarism and impaired serum ANP regulation were observed.

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