Glucocorticoid-Induced Central Diabetes Insipidus in a Case of Malignant Lymphoma

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OTA, M., KIMURA, T., OTA, K., SHOJI, M., INOUE, M., SATO, K., YAMAMOTO, T., ENDO, K., NARITA, M., ABE, K. and YOSHINAGA, K. Glucocorticoid-Induced Central Diabetes Insipidus in a Case of Malignant Lymphoma. Tohoku J. Exp. Med., 1991, 163 (4), 245-254 — A 37-year-old man was diagnosed as malignant lymphoma infiltrating in the central nervous system with hypopituitarism and secondary glucocorticoid deficiency. In this case, plasma arginine vasopressin (AVP) increased, but glucocorticoid administration decreased plasma AVP and increased urine volume with a reduction in urinary osmolality, indicative of the presence of glucocorticoid-induced diabetes insipidus. At the terminal stage, plasma AVP did not increase in response to the withdrawal of glucocorticoid and urine volume remained decreased, suggesting the presence of masked diabetes insipidus. Autopsy showed an infiltration of lymphoid cells around the cerebral ventricles and necrosis in the hypothalamo-hypophyseal system. These findings suggested that glucocorticoid might centrally play an important role in the regulation of AVP release, and its deficiency potentiated AVP release. ——— AVP; leukemia; hypopituitarism; hyponatremia; hypernatremia

It is well known that leukemia and chronic granulomatous diseases may infiltrate in the brain, impairing the hypothalamo-hypophyseal system, thereby inducing central diabetes insipidus and hypopituitarism. However, the incidence of central diabetes insipidus complicated in leukemia and lymphoma has been reported to be relatively low (Williams et al. 1958; Miller and Campbell 1971). To our knowledge, there have been only a few cases with central diabetes insipidus

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due to malignant lymphoma (Williams et al. 1958).

Recently, we observed a rare case of central diabetes insipidus and hypopituitarism due to malignant lymphoma. In this patient administration of glucocorticoid blocked the release of arginine vasopressin (AVP) to elicit central diabetes insipidus. After stopping glucocorticoid, the release of AVP restored. And finally, AVP release subsided in the absence of glucocorticoid to become a state of masked diabetes insipidus. The purpose of this paper is to report the clinical course of the patient and to discuss the pathophysiology of the inhibition of AVP release by glucocorticoid.

PATIENT AND METHODS

A 37-year-old man, suffering from nausea, headache, vomiting and the impairment of consciousness, was admitted to the department of internal medicine of Tohoku University Hospital under the diagnosis of malignant lymphoma on December 26, 1988.

In 1984, he noticed a tumor in the right upper eye lid, and was diagnosed as follicular lymphoma. However, at that time involvement of the other organs was not found by Ga and Te scintigrams.

In February, 1985, urine incontinence and gait disturbance occurred. The diagnosis of the spinal cord tumor (Th5) was made and the resection of the tumor was performed in the department of orthopedics in our hospital. The histology of the tumor was diffuse large cell lymphoma. Thereafter, he was treated with cyclophosphamide, vincristine, mercaptopurine and prednisolone, but gradually deteriorated to a state of disorientation and impaired consciousness. On December 25, 1988, he was transferred to our department to be treated more intensively. At this time, the consciousness was stupor, blood pressure 84/54 mmHg, heart rate 55/min, and temperature 35.5°C.

The heart and lung were not remarkable without cardiac murmur and rales. Abdomen was flat and soft and liver, spleen, and kidneys were not palpable. No edema in the pretibial regions. No enlargement of lymphnodes in the neck, axillar and femoral regions. Patellar and Achilles' tendon reflex normal. He had 3.8 × 10¹²/liter of red blood cell with 148 g/liter of hemoglobin, and 0.44 of hematocrit, and 6.7 × 10⁹/liter of white blood cell without abnormal findings in its composition. In urinalysis, proteinuria, glycosuria, and occult blood were not noticed, and sediment was not remarkable either. Liver function tests were, aspartate aminotransferase (AST) 0.38, alanine aminotransferase (ALT) 0.83, LDH 7.30, and alkaline phosphatase 3.25 μkat/liter. Hbs-Ag and Hbs-Ab were negative. Serum total protein was 58 g/liter with 0.75 albumin, 0.02 α₂-globulin, 0.06 β-globulin, 0.08 γ-globulin. Total cholesterol was 4.35, phospholipid 62.00 and triglyceride 0.68 mmol/liter. Fasting blood sugar was 6.2 mmol/liter. Serum Na was 136, K 4.6 and Cl 100 mmol/liter. Serum creatinine, BUN and uric acid were 60 μmol/liter, 2.0 mmol/liter, and 286

<table>
<thead>
<tr>
<th>Table 1. Endocrinological</th>
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<tr>
<td>T&lt;sub&gt;3&lt;/sub&gt; (nmol/liter)</td>
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<tr>
<td>0.69</td>
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<td>(1.08–2.76)</td>
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T<sub>3</sub>, plasma triiodothyronine; T<sub>4</sub>, plasma thyroxine; FT<sub>4</sub>, free thyroxine; TSH, tisol; 17-OHCS, 17-hydroxycorticosteroid; 17-KS, 17-ketosteroid; P<sub>AVP</sub>, plasma AVP;
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Creatinine clearance was 1.28 ml/sec and PSP 44% (15 min). ECG revealed normal sinus rhythm. Brain computed tomography (CT) (Fig. 1) showed an enlargement of the lateral ventricles and the remarkable enhancement of contrast material along the wall of the lateral and 3rd ventricles, suggesting the presence of hydrocephalus due to the obstruction of the aquaeductus cerebri. These abnormal findings markedly improved after an irradiation to the brain.

In endocrinological examinations (Table 1), thyroid stimulating hormone (TSH) did not markedly, despite a fall in serum T3 and T4 levels. Daily urinary 17-OHCS, 17-KS and

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<tr>
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<th>17-OHCS (μmol/day)</th>
<th>17-KS (μmol/day)</th>
<th>PAVP (pmol/liter)</th>
<th>UAVP (pmol/day)</th>
<th>CSFAVP (pmol/liter)</th>
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<tbody>
<tr>
<td>5</td>
<td>6</td>
<td>1.7</td>
<td>62.4</td>
<td>4.2</td>
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<td>(19-63)</td>
<td>(10-21)</td>
<td>(1.4-6.5)</td>
<td>(53.3-163.2)</td>
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Data

thyroid stimulating hormone; ACTH, adrenocorticotropic hormone; CS, plasma cor-

UAVP, urine AVP; CSFAVP, cerebrospinal fluid AVP. Parenthesis; normal range.
AVP outputs, plasma cortisol, ACTH and AVP were all decreased. AVP in the cerebrospinal fluid was greater than plasma AVP.

As shown in Fig. 2, he received an irradiation (total 45 Gray) to the whole brain every the other day for about one month, and glycerol and dexamethasone were administered to prevent brain edema during the first several days. These treatments resulted in an improvement of consciousness. His body fluid balance was maintained by daily parenteral administration of 2,000–2,500 ml of fluid containing electrolytes, glucose and amino acids. Serum Na and plasma osmolality tended to decrease with a rise in urinary osmolality for initial 10 days. Thereafter, his consciousness started to deteriorate again and glycerol and dexamethasone were again initiated. On day-17, serum Na and plasma osmolality were increased to 160 mmol/liter and 320 mmol/kg, respectively. And hourly urine flow rate suddenly increased to more than 200 ml, accompanied by a fall in urinary osmolality (less than 200 mmol/kg), and then 2.5 μg of desmopressin (DDAVP) was administered to control urine volume under the diagnosis of central diabetes insipidus. Several hours after DDAVP treatment, plasma AVP was found paradoxically high, 49.4 pmol/liter and urinary osmolality still remained hypertonic with decreased urine volume on the next day.

![Clinical course of the patient](image)

Fig. 2. Clinical course of the patient. P<sub>Na</sub>, plasma Na concentration; Posm, plasma osmolality; Uosm, urinary osmolality; UV, daily urine volume; P<sub>AVP</sub>, plasma AVP; DDAVP, desmopressin; IVH, intravenous hyperalimentation; DIV, drip intravenous infusion; C-R, Carter-Robbins test; D-P, dehydration-pitressin test; WL, water load test of 20 ml/kg body weight; i.v., intravenous administration; p.o., per os administration.
Fig. 3. Relationship between plasma osmolality (Posm) and plasma AVP (P_{AVP}).
- with glucocorticoid; ○, without glucocorticoid; [], normal range.

Fig. 4. Carter-Robbins test. C_{H2O}, free water clearance; Cosm, osmolar clearance; UF, urine flow rate; HS, 2.5% hypertonic saline infusion (0.24 ml/kg body weight for 45 min) The other abbreviations are the same as Figs. 2 and 3.
TABLE 2. *Dehydration with either DDAVP or Pitressin test*

<table>
<thead>
<tr>
<th>Time</th>
<th>BW (kg)</th>
<th>Posm (mmol/kg)</th>
<th>Uosm (mmol/kg)</th>
<th>UF (ml/min)</th>
<th>P_{AVP} (pmol/liter)</th>
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<tbody>
<tr>
<td>On March, 31, 1989</td>
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<tr>
<td>0000</td>
<td>308</td>
<td>199</td>
<td>3.3</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>DDAVP 2.5 μg (nasal)</td>
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<tr>
<td>0300</td>
<td>314</td>
<td>615</td>
<td>0.5</td>
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<tr>
<td>0600</td>
<td>315</td>
<td>669</td>
<td>0.9</td>
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<td>1200</td>
<td>310</td>
<td>735</td>
<td>0.2</td>
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<td>On January, 13, 1990</td>
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<td>63.0</td>
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<td>1200</td>
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<td>145</td>
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<tr>
<td>1400</td>
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<td>5.5</td>
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<td>1415</td>
<td>300</td>
<td>147</td>
<td>3.3</td>
<td>20.2</td>
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<tr>
<td>1430</td>
<td></td>
<td>246</td>
<td>0.7</td>
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BW, body weight; Posm, plasma osmolality; Uosm, urinary osmolality; UF, urine flow rate; P_{AVP}, plasma AVP; DDAV, desmopressin.

Fig. 5. Acute water load test (20 ml/kg·b.w.) with glucocorticoid (A) and without glucocorticoid (B). The abbreviations are the same as Fig. 4.
same day (day-18), the response of urinary osmolality to water deprivation was quite normal, but plasma AVP was relatively low compared to plasma osmolality (Table 1).

On day-20, he was diagnosed as hypopituitarism because of decreased plasma cortisol, and dexamethasone replacement (0.5 mg/day) was again initiated. However, immediately after the treatment, polyuria suddenly occurred and DDAVP was again started. Plasma AVP was less than 1.4 pmol/liter and plasma osmolality and urine volume were maintained within normal range after these regimens.

Fig. 6. Histology of the brain. The infiltration of lymphoid cells in the thalamus (A, H-E *100) and necrosis around the 3rd and lateral ventricule including the supraoptic and paraventricular nuclei (B, H-E *50).
In order to know the effect of glucocorticoid on the release of AVP, dexamethasone was with held for 2 days from day-29 to -30 as well as day -39 to -40 and for one day on day-150. During these periods, cardiovascular dysfunction and dehydration were not observed. Plasma AVP was markedly elevated during the initial 2 periods (more than 188 and 178 pmol/liter, but not at the last period. On the other hand, plasma AVP remained low while dexamethasone was administered. There was no significant correlation between plasma osmolality and plasma AVP in these periods, and remarkable rises in plasma AVP were noticed during the absence of glucocorticoid replacement (Fig. 3). Carter-Robbins (Fig. 4, day-90) and dehydration pitressin tests (Table 2, day-96) during dexamethasone were compatible with central diabetes insipidus, because increased plasma osmolality due to these procedures neither stimulated AVP release nor increased urinary osmolality. Moreover, an acute water load test (20 ml/kg BW) was performed twice with (day-130) and without glucocorticoid (day-150). A rise in free water and osmolar clearances in response to water loading without glucocorticoid (Fig. 5B) was smaller than that after its replacement (Fig. 5A), indicative of the presence of masked diabetes insipidus. However, in these tests, still a small amount of AVP was detectable in the basal level. Especially, plasma AVP decreased in response to a fall in plasma osmolality after glucocorticoid, but this relation was lost after the withdrawal of the drug with a sporadic increase in plasma AVP.

He had been well under treatment with DDAVP and dexamethasone for over than 10 months, but malignant lymphoma in the brain recurred in February 1990. He finally died of the respiratory failure in March 1990, and autopsy showed that lymphatic cells were diffusely infiltrated into the thalamus (Fig. 6A) and necrotic tissues were found around the 3rd and lateral ventricles including suprapotic and paraventricular nuclei (Fig. 6B).

AVP in the blood, urine and CSF was extracted using a resin-microcolumn and assayed by a previously reported radioimmunoassay (Kimura et al. 1980). The other hormones were determined by respective commercial kits.

**DISCUSSION**

In the present case, the lesions in the hypothalamoneurohypophyseal system produced by malignant lymphoma provoked diabetes insipidus after glucocorticoid administration for the treatment of hypopituitarism in the early stage, and withdrawal of glucocorticoid brought about a marked rise in plasma AVP. However, in the later stage, the removal of the drug had no longer any effect on AVP release, but its replacement further potentiated a rise in urine volume with further fall in plasma AVP, indicating the presence of masked diabetes insipidus. These results indicate that, in the early stage, the vasopressin neurons had a capability of synthesizing and secreting AVP in response to various stimuli, but glucocorticoid replacement interfered with AVP release, thereby resulting in diabetes insipidus, and the progress of the disease gradually and more extensively impaired the hypothalamus with the resultant loss of ability to secrete AVP.

Secondary diabetes insipidus was known to occur in the hypothalamic lesions due to brain tumor, head trauma, leukemia and granulomatous diseases. Williams et al. (1958) reported that there was one diabetes insipidus out of 1864 patients with leukemia or lymphoma. Blotner (1958) showed that only 2 cases out of 124 patients with diabetes insipidus were caused by leukemia. In particular, Miller and Campbell (1971) reviewed literature concerning diabetes insipidus due to leukemia and reported that 20 cases of diabetes insipidus were associated
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with leukemia. To our knowledge, no patient like the present case has never been reported. As to the histology in the previously reported cases (Rosenzweing and Kendall 1966; Miller and Campbell 1971), there have been noticed an infiltration of leukemic cells, hemorrhage, and necrosis in the neurohypophysis and hypothalamo-hypophyseal tract. Indeed, in the present case, there were a large amount of lymphoid cells in the area surrounding the 3rd and lateral ventricles and massive necrosis was also noticed in the hypothalamus. Therefore, it is probable that these lesions impaired the hypothalamo-hypophyseal system, causing the abnormalities described above.

Glucocorticoid per se has been reported to suppress directly the vasopressin-secreting neurons and/or to attenuate volume- and baro-receptor reflex-mediated AVP release (Schrier and Linas 1980). Dingman et al. (1958) suggested that the hypersecretion of AVP occurred in glucocorticoid deficit secondary to hypopituitarism with subsequent hyponatremia and an impaired urinary dilution, and glucocorticoid restored these derangements to normal. Moreover, Boykin et al. (1978) showed that plasma AVP was elevated in mineralcorticoid-replaced adrenalectomized dogs even in a situation of lowered plasma osmolality induced by an acute water load, and glucocorticoid administration normalized the AVP response to hemodilution associated with a rise in cardiac output and blood pressure, suggesting the participation of the hemodynamic reflex-mediated suppression of AVP release. In the present case, the removal of glucocorticoid markedly increased plasma AVP, despite that there was no evidence of cardiovascular collapse and dehydration. Therefore, this is not due to hemodynamic changes, but rather may be due to the central mechanisms such as glucocorticoid-mediated disinhibition of AVP release. Healy et al. (1985) also showed that anti-glucocorticoid, RU 486, stimulated AVP and ACTH release, and pretreatment with dexamethasone blocked the effect of RU 486.

Taken together, in the present case, it is likely that the hyperactivity of AVP-secreting neurons elicited by the damage of the inhibiting neurons by lymphoma and/or the direct stimulation of malignant cells to vasopressin neurons may play some roles in the nonosmotic release of AVP in response to various stimuli, and glucocorticoid per se may act to directly attenuate the hyperactivity of vasopressin neurons or to indirectly block AVP release via some putative neurons. On the other hand, hypothyroidism has also been reported to stimulate AVP release (Goldberg and Reivich 1962; Pettinger et al. 1965). However, this patient was not the case because AVP release subsided by the replacement of glucocorticoid.

In the present case, the AVP response to glucocorticoid deficiency was disappeared as the disease progressed, but the weak AVP response to changes in plasma osmolality was still observed, though the patient had already been in a state of diabetes insipidus. These results also suggest that increases in urine volume observed in masked diabetes insipidus after glucocorticoid therapy may be
partly explained by the suppression of AVP release, besides its direct renal hemodynamic effect (Kleeman et al. 1964; Green et al. 1970).

In conclusion, in the present case, the hypothalamic lesions due to malignant lymphoma caused diabetes insipidus associated with glucocorticoid-induced suppression of AVP release, and its removal partially restored AVP secretion. These results are compatible with the concept that glucocorticoid may act physiologically to suppress AVP release in a central mechanism.

Acknowledgments

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References