Increased Renal Kallikrein Excretion in SIADH after Vincristine Therapy

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Abstract

This is a report about a 14-year old girl who, following chemotherapy for malignant teratoma, developed a clinical state of SIADH (syndrome of inappropriate secretion of antidiuretic hormone).

The causative agent was most likely vincristine (VCR). The important feature in this case was that the urinary kallikrein activity was high when she was affected by SIADH and decreased when her hyponatremia improved. Sodium clearance was significantly correlated with the increase in urinary kallikrein activity. It is considered that the kallikrein-kinin system may in part participate in the excessive natriuresis of SIADH.

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH), occurring after vincristine (VCR) therapy, has been well recognized. About 20 cases of SIADH due to VCR have been reported since Fine (Fine, et al., 1966) reported on the hyponatremia and excessive renal sodium loss in an 11-month-old boy treated for rhabdomyosarcoma. The mechanism of persistent sodium loss in spite of profound hyponatremia in SIADH is unclear, though several hypotheses such as an increase in GFR (glomerular filtration rate), a decrease in aldosterone secretion, and a so-called “third factor” have been proposed (Meldonado et al., 1980). In addition, the role of the kallikrein-kinin system or prostaglandin system has not been fully studied in SIADH. In this report, the kallikrein-kinin system was investigated in one patient with SIADH.

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Case report

A 14-year-old girl was surgically operated on for a malignant teratoma of the right ovary. After excision of the tumor, 1.5 or 2.0 mg of VCR was administered once a week starting April 9. The patient was treated with 200 mg of cyclophosphamide daily for 5 days starting May 21 and 400 µg of dactinomycin daily for 5 days starting May 23. The serum sodium concentration decreased from 132 mEq/l to 128–129 after the administration of these drugs. The patient complained of headache and weariness from June 4. There was no peripheral edema or signs of dehydration. The patellar and achilles tendon reflexes were absent. The hematocrit reading was 29%. The serum levels of chloride and potassium were 93 mEq/l and 3.9 mEq/l respectively and the urinary sodium concentration was 134 mEq/l. The serum osmolality was 257 mosm/kg, and the urine osmolality was 652
Table 1. Laboratory data

(Hematological Examination)

RBC 360×10^12/mm^3
Hb 10.2 g/dl
Ht 29%
WBC 3300 /mm^3
Reticulocyte 28 \%
Platelet 20×10^11/mm^3

(Urinalysis)

PH 6
Protein (-)
Glucose (-)
Occult-blood (-)
Urobil (+)

[Blood Chemistry]

Na 129 mEq/l
K 3.9 mEq/l
Cl 93 mEq/l
BUN 5 mg/dl
Serum Cr 0.5 mg/dl
T.P. 7.0 g/dl
Alb. 4.0 g/dl
Osmolality 248 mOsm/kg

(Urine Chemistry)

Na 134 mEq/l
K 32 mEq/l
Cl 98 mEq/l
Cr. 48 mg/dl
Osmolality 791 mOsm/kg

(BP)

120/70 mmHg

Table 1. Laboratory data

(Renal Function)

Ccr 88.8 ml/min
PSP
T1 15 min 35%
T1 30 min 45%
T1 60 min 60%
Fishberg
T1 1020
T1 1021

[Thyroid Function]

T1 15.7 \( \mu \)g/dl
T1 150 ng/dl
T1.U 24.6

[Hypothalamo-Adrenal Function]

1. Metyparone test

<table>
<thead>
<tr>
<th>Urinary 17-OHCS (mg/day)</th>
<th>17-KS (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>before 1</td>
<td>2.0</td>
</tr>
<tr>
<td>2</td>
<td>2.6</td>
</tr>
<tr>
<td>after 3</td>
<td>7.4</td>
</tr>
<tr>
<td>4</td>
<td>38.3</td>
</tr>
</tbody>
</table>

2. Rapid ACTH-Test

<table>
<thead>
<tr>
<th>Serum cortisol (( \mu )g/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>before</td>
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<tr>
<td>after</td>
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</table>

mosm/kg. The urinalysis results were within normal limits. The renal, peripheral thyroid and hypothalamic-adrenal functions were within normal limits (Table 1). Only 14\% of the oral water load was excreted in 4 hours according to a water-loading test. From these observation the patient’s condition was diagnosed as SIADH. Restricting the fluid intake to less than 600m/day resulted in a progressive rise in the serum sodium level to 144 mEq/l after 12 days. The headache disappeared. The patient lost about 2 kg in body weight during this period. The serum sodium again decreased to 132 mEq/l on July 2, following only VCR (tenth) administration.

Fig. 1. Values for the hormones related to the body fluid regulatory mechanism

*Orthostatic position
PRA : Plasma renin activity
ADH : Antidiuretic hormone

<table>
<thead>
<tr>
<th>VCR therapy</th>
<th>June</th>
<th>12</th>
<th>14</th>
<th>16</th>
<th>18</th>
<th>20</th>
<th>25 July 7</th>
<th>August</th>
<th>8</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum sodium (mEq/l)</td>
<td>128</td>
<td>127</td>
<td>132</td>
<td>136</td>
<td>144</td>
<td>132</td>
<td>135</td>
<td>141</td>
<td>139</td>
<td>138</td>
</tr>
<tr>
<td>Plasma osmolality (mOsm/kg)</td>
<td>257</td>
<td>268</td>
<td>284</td>
<td>269</td>
<td>299</td>
<td></td>
<td></td>
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<tr>
<td>PRA (ng/ml/hr)</td>
<td>1.57–4.04</td>
<td>1.31</td>
<td>2.45–4.73</td>
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<td></td>
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<td></td>
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<tr>
<td>Aldosterone (ng/dl)</td>
<td>12.2–23.0</td>
<td>7.3</td>
<td>3.88–3.15</td>
<td></td>
<td></td>
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<tr>
<td>Plasma ADH (pg/ml)</td>
<td>3.9</td>
<td>3.0</td>
<td>0.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Angiotensin I (pg/ml)</td>
<td>50</td>
<td>65</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>Angiotensin II (pg/ml)</td>
<td>15</td>
<td>44</td>
<td></td>
<td></td>
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<table>
<thead>
<tr>
<th>Urinary sodium (mEq/day)</th>
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<tr>
<td>62</td>
</tr>
<tr>
<td>51</td>
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</table>
Hormones related to the body fluid regulatory mechanism

Several hormones were studied during the clinical course (Fig. 1). Urinary kallikrein activity was measured fluorometrically using Pro-Phe-Arg-MCA as substrates (Morita et al., 1977). Plasma ADH levels were measured by radioimmunoassay (Shimizu et al., 1978). As shown in Figure 1, when the SIADH was prominent, the serum sodium concentration was 127 mEq/l, the plasma ADH concentration was 3.9 pg/ml, plasma aldosterone was 12.2 ng/dl and the urinary kallikrein excretion was about 180 μmole·min/day. Two months later, when the serum sodium concentration had improved to 141 mEq/l, the plasma ADH level had decreased to 0.4 pg/ml, the plasma aldosterone concentration had decreased to 3.88 ng/dl and the urinary kallikrein excretion had decreased to about 80 μmole·min/day. The levels of plasma renin activity, plasma prostaglandin E, Prostaglandin F₂α and angiotensin I and II were within normal limits and did not change significantly between the two periods. There was no significant difference in urine volume or urinary osmolality, and there was no relationship between urinary kallikrein excretion and urine volume. As shown in Fig. 2, there was a significant relationship between urinary kallikrein excretion and sodium clearance (Fig. 2).

Discussion

From 1966 to 1980, about 20 cases of SIADH induced by VCR were reported. Hyponatremia occurred within 40 to 10 days following the VCR administration and lasted 8 to 10 days (Moses et al., 1974). In the present case, hyponatremia became evident after the ninth period of VCR in a cumulative dosage of 15.5 mg and cyclophosphamide administration. The serum sodium concentration increased when the VCR discontinued, and decreased again when only VCR was resumed. Cyclophosphamide has been reported to induce an impairment of water excretion in a dose greater than 50 mg/kg body weight or 1500 mg/m² (Defronzo et al., 1973; Block et al., 1968). Plasma osmolality decreased from 4 to 12 hours and lasted up to 20 hours following the administration of the drug. In our case, however, the dose of cyclophosphamide administered was less than the critical dose mentioned above. Cyclophosphamide was not administered in the second period of hyponatremia. Therefore, VCR seemed to be the most probable cause of SIADH in this case. Although the mechanism of SIADH caused by VCR has not been clarified, it is probably related to the direct neurotoxic effect of the drug on the hypothalamus, the neurohypophyseal tract or the posterior pituitary itself. This hypothesis is proposed by Rufener using rats (Rufener et al., 1972) and in view of the fact that most patients with VCR-induced SIADH have also manifested signs of neurotoxicity, which were also seen in our patient. Persistent urinary sodium loss in spite of profound hyponatremia is one of the characteristic features of SIADH. But the mechanism responsible for the natriuresis in SIADH is unknown. As factors of
natriuresis, the prostaglandin or kallikrein-kinin system can be considered. Because there is no established data about kallikrein excretion in SIADH, we studied the urinary kallikrein in our patient. When the state of SIADH with increased urinary excretion of sodium was first noticed, the patient’s excretion of urinary kallikrein was high. However, it became normal after water restriction and discontinuation of VCR for one month. This suggests that natriuresis in SIADH may be related to the increased activity of the kallikrein-kinin system. As factors which stimulate urinary kallikrein excretion in this case, ADH, aldosterone, volume expansion and VCR itself could be considered. The effect of ADH on urinary kallikrein secretion has been variously reported. Some reports (Fejes-Töth et al., 1980) on animal studies have indicated that ADH administration was related to increased kallikrein excretion, while other reports (Mills et al., 1980) negated this. The increase in kallikrein excretion can be caused by hyperaldosteronism, but no conclusion has been reached yet as to whether this was due to the action of aldosterone directly or secondarily due to the hyperaldosterone-induced increase in body fluid (Carretero et al., 1976; Rabit et al., 1979; Adetuyibi and Mills, 1972; Margolous et al., 1974; Seino et al., 1977; Kaizu and Margolius, 1975). There has been no report indicating that VCR stimulated urinary kallikrein excretion. There is little possibility of VCR directly increasing urinary kallikrein excretion. In this case, when the level of hyponatremia was prominent, the plasma ADH level was inappropriately high (3.9 pg/ml) compared with the plasma osmolality, and the plasma aldosterone concentration was within the normal range (12.2 ng/dl), and body weight increased about 2 kg. We could not find any significant relationship between urinary kallikrein excretion and either plasma ADH nor aldosterone levels, probably because of the short period of hyponatremia. From the significant relationship between urinary kallikrein excretion and sodium clearance, it is speculated that the increase in urinary sodium excretion in spite of profound hyponatremia in this patient may be caused by increased kallikrein activity.

Acknowledgements

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References


