

Involvement of Arginine Vasopressin and Renal Sodium Handling in Pathogenesis of Hyponatremia in Elderly Patients

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Abstract. The present study was undertaken to determine the pathophysiological role of arginine vasopressin (AVP) in elderly patients with hyponatremia, and the efficacy of fludrocortisone acetate in treating their hyponatremia. Eleven hospitalized patients aged 65 years or older whose serum sodium levels were less than 130 mEq/l were examined. The hyponatremic patients included two groups of patients: syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and central salt-wasting syndrome. And 24 healthy, young subjects aged 20 to 34 years, and 24 healthy, elderly subjects aged 65 to 80 years were recruited by community announcement. The elderly subjects had decreased urinary concentrating ability and exaggerated response of AVP secretion to osmotic and nonosmotic stimuli, as compared to the young subjects. All the patients had hyponatremia, with the exaggerated urinary loss of Na. Plasma AVP levels were elevated despite hypoosmolality in all the 2 groups of hyponatremic, elderly patients. Plasma renin activity and plasma aldosterone concentrations were low in the patients with SIADH and central salt-wasting syndrome. Fludrocortisone acetate therapy was effective in the patients with central salt-wasting syndrome and 3 patients with SIADH whose hyponatremia remained unchanged after water restriction. Water restriction therapy normalized serum Na levels in only 3 patients with SIADH. These results indicate that AVP is involved in the mechanism for hyponatremia in the elderly patients with SIADH and central salt-wasting syndrome. Severe hyponatremia associated with SIADH and central salt-wasting syndrome responds well to mineralocorticoid therapy. Both the secretion of AVP and renal sodium handling may be involved in the mechanisms of action of the disorders. The diagnostic criteria for SIADH in the elderly patients may have to be reevaluated and should be considered to indicate fludrocortisone acetate therapy.

Key words: Hyponatremia, Arginine vasopressin, Renal sodium handling, SIADH, Central salt-wasting syndrome, Fludrocortisone acetate

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HYPONATREMIA may occur in association with increased, decreased or normal amounts of body fluid [1]. Hypovolemic hyponatremia results from renal or extrarenal loss of sodium (Na), but is a minor cause of hyponatremia. In contrast, dilu-

tion of extracellular Na by increased body fluid seems to lead to hyponatremia in most clinical settings.

After intracranial disorders the disturbance of renal Na handling appears in elderly subjects, and results in hyponatremia with exaggerated renal loss of Na and blood volume contraction. This seems to be distinct from the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), because hypovolemia is not related to SIADH [2]. Other factors producing natriuresis seems to be involved

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in the mechanisms of hyponatremia [3]. This kind of hyponatremia has been called "central salt-wasting syndrome" [4–8], the causes of which appear to be multifactorial. We reported three patients with hyponatremia after head injury, and the increase in arginine vasopressin (AVP) from the neurohypophysis plays a key role in leading to hyponatremia [9]. We have found that patients, who diagnosed as having SIADH, can not easily respond to water restriction therapy to normalize serum Na levels. Such SIADH patients seem to be distributed in elderly subjects, because the compensatory ability to conserve Na or water may be reduced in elderly subjects [10].

In the present study we analysed 11 hyponatremic patients aged 65 years or older, and they included two groups of hyponatremia derived from SIADH and central salt-wasting syndrome. We evaluated the pathophysiological role of AVP in hyponatremia and the efficacy of fludrocortisone acetate in elderly patients with central salt-wasting syndrome and SIADH. In addition, whether age influences AVP secretion in response to osmotic and non-osmotic stimuli was examined.

Subjects and Methods

Eleven elderly patients with SIADH and central salt-wasting syndrome were examined between October, 1980 and September, 1993. We selected the patients whose serum Na levels were less than 130 mEq/l. They were 7 males and 4 females whose ages were 65 years or older. They were

admitted to Jichi Medical School Hospital because of various reasons. Some patients complained of the disturbance of consciousness, generalized malaise or fatigue. The others were to have evaluated hyponatremia further.

Six patients with SIADH had hyponatremia, hypoosmolality, exaggerated urinary excretion of Na, hypertonic urine and normal renal and adrenal functions (Table 1). And physical findings showed neither dehydration nor edema. SIADH occurred in 3 patients after cerebral infarction, in 2 patients after head trauma and in one patient in whom the cause was considered idiopathic. Serum Na levels ranged from 109 to 125 mEq/l when hyponatremia was discovered. In five patients with central salt-wasting syndrome, hyponatremia was associated with hypoosmolality, hypertonic urine and persistently increased urinary loss of Na (Table 2). It is unlikely that renal and adrenal functions were poor enough to have caused a massive renal loss of Na. Adrenocorticotrophic hormone (ACTH), cortisol and thyroid hormones were all within the normal ranges. Physical findings including dry skin, dry tongue, and decreased body weight, suggested the presence of dehydration in 4 of 5 patients. Three of 5 patients had had head injury 1–4 weeks before hyponatremia was manifested [9]. Such accidents were closely related to the onset of hyponatremia, because two patients were confirmed to have had normal values of serum Na when they got head trauma. In two other patients there was no particular matter related to the occurrence of hyponatremia.

We analyzed the relationship between serum Na

Table 1. Laboratory values at hospitalization for 6 elderly patients with SIADH

		Patient					
		1	2	3	4	5	6
Age, Sex		66M	79F	77M	65M	72M	65F
Serum Na	mEq/l	119	124	109	109	125	124
Serum K	mEq/l	4.5	4.4	3.3	4.0	3.8	4.0
Serum Cl	mEq/l	87	88	69	68	86	91
Blood urea nitrogen	mg/dl	8	19	8	7	13	12
Serum uric acid	mg/dl	2.9	3.5	1.1	2.6		1.7
Plasma osmolality	mOsm/kg H ₂ O	257	266		238	268	267
Urinary sodium	mEq/day	214	201	132	169		143
Urinary potassium	mEq/day	32	34	30	42		44
Plasma renin activity	ng/ml/h	3.20	1.01	1.41	1.37	0.89	1.48
Plasma aldosterone	ng/dl	5.7	10.5	2.8	4.2	2.4	4.9
Plasma arginine vasopressin	pg/ml	3.4	0.7	1.9	2.4	1.0	2.4

Table 2. Laboratory values at hospitalization for 5 elderly patients with central salt-wasting syndrome

		Patient				
		1	2	3	4	5
Age, Sex		86M	71F	79M	71M	78F
Serum Na	mEq/l	117	106	129	105	109
Serum K	mEq/l	5.1	4.7	4.0	4.2	3.9
Serum Cl	mEq/l	82	66	93	67	71
Blood urea nitrogen	mg/dl	10	15	6	8	15
Serum uric acid	mg/dl	2.5	0.3	1.6	0.6	1.1
Plasma osmolality	mOsm/kg H ₂ O	254	234	271	228	247
Urinary sodium	mEq/day	225	240	177	324	132
Urinary potassium	mEq/day	14	66	29	53	32
Plasma renin activity	ng/ml/h	0.1	0.5	0.4	0.3	1.4
Plasma aldosterone	ng/dl	1.5	2.8	4.2	5.5	2.8
Plasma arginine vasopressin	pg/ml	4.2	3.9	4.6	6.8	1.9

levels and plasma AVP levels. Also, we compared the changes in plasma AVP levels with that in circulatory blood volume estimated clinically [11]. Percent changes in circulatory blood volume was determined using changes in hematocrit (Ht); $(Ht_1 - Ht_2)/Ht_2 \times 100$ (%).

Urine concentration and AVP secretion studies

Urine concentrating ability and AVP release were examined in two groups of healthy volunteers, including the elderly group aged 65 to 80 years and the young group with age of 20 to 34 years. We obtained informed consent from all the volunteers to join the present protocols. The following four studies were examined in different subjects in each group. (A) Fishberg test: Water drinking was prohibited at least 12 h after the last supper, and in the early morning three urine collections were made at 1-h intervals to measure urinary osmolality (Uosm). (B) 1-Deamino-8-D-arginine vasopressin (DDAVP) test: After urine and blood collections were made, water (15 ml/kg body weight) was given orally for 30 min. Ten μ g DDAVP was given intranasally, and thereafter 4 one-hour urine collections were made to measure urine volume and Uosm. Water drinking was forced in the same volume as urine volume at each time when urine was collected. (C) Hypertonic saline test: After urine and blood collections were made, hypertonic saline (5% NaCl) was infused intravenously at a rate of 0.05 ml/kg/min for 120 min. Blood was collected at 30 min intervals for

120 min to measure plasma osmolality (Posm) and plasma AVP levels. (D) Tilting test: Subjects had had a sodium intake of 8 g/day for a week. Subjects were placed in the supine position on a tilt table, and a venous catheter was inserted through a cubital vein. Thirty min later, the subjects were kept in place at 60° head-up tilt for 20 min, and thereafter they were placed in the supine position again. During the 90 min observation period, blood pressure and heart rate were determined at 5 min intervals. Also, Posm, plasma AVP levels and plasma renin activity (PRA) were determined at 10 min intervals.

Hormonal assays

Blood was collected in chilled tubes containing EDTA-Na₂ (1 mg per ml blood) and centrifuged at 3000 rpm at 4 °C for 15 min. The supernatants were decanted and frozen at -20 °C until the time of assay for plasma AVP, aldosterone, and PRA. Plasma AVP was measured by RIA with AVP RIA kits (Mitsubishi Yuka Co., Tokyo, Japan) [12, 13]. PRA and plasma aldosterone concentrations were determined by RIA with PRA RIA kits (Midori-Juji Co., Tokyo, Japan) and Aldosterone RIA kits (Dainabott Lab., Tokyo, Japan) [14, 15]. The normal value of plasma AVP is 0.2–2.2 pg/ml, that of PRA 0.3–2.9 ng/ml/h, and that of plasma aldosterone 1.1–6.3 ng/dl. The data were subjected to an analysis of multiple variance and Neuman-Keuls' range test. $P < 0.05$ was considered significant.

Results

Serum Na levels and plasma AVP levels at a hospitalization of the 11 patients are shown in Tables 1 and 2. Following our definition, serum Na levels were below 130 mEq/l in all the patients. Plasma AVP levels of the SIADH patients were comparable to those of 1.4 ± 0.2 pg/ml of the control subjects aged 18 to 63 years ($n=20$), and they seem to be less than those of patients with central salt-wasting syndrome. Plasma AVP levels were detectable by RIA in all the patients, though serum Na levels were reduced as mentioned above.

The relationship between plasma osmolality and plasma AVP levels is shown in Fig. 1. The shaded area means the normal relationship of the control subjects. As seen apparently, all the plots shift to the left. Plasma AVP levels were not sufficiently suppressed despite hypoosmolality in 2 groups of patients. Because plasma AVP levels should be suppressed to below 0.5 pg/ml in normal subjects if Posm is less than 280 mOsm/kg H₂O [16]. Particularly, the patients with central salt-wasting syndrome had relatively high levels of plasma AVP in spite of their serious hypoosmotic condition.

We analyzed the urinary concentrating ability and AVP secretion in normal volunteers. Fishberg test showed the urinary concentrating ability. The maximal Uosm was 620.6 ± 74.1 mOsm/kg H₂O in the elderly group, a value less than that of 904.4 ± 48.5 mOsm/kg H₂O in the young group ($P<0.05$). The results of the DDAVP test are: Uosm after the oral water intake (15 ml/kg body wt) was significantly higher in the elderly group than that in the

young group (315.3 ± 69.2 vs. 115.2 ± 22.6 mOsm/kg H₂O, $P<0.05$). However, after the DDAVP administration the increase in Uosm was less in the elderly group than in the young group, as the maximal Uosm were 487.8 ± 82.5 and 828.7 ± 55.7 mOsm/kg H₂O in the elderly and young groups, respectively ($P<0.05$).

The response of AVP secretion to hypertonic saline infusion is shown in Table 3. Plasma

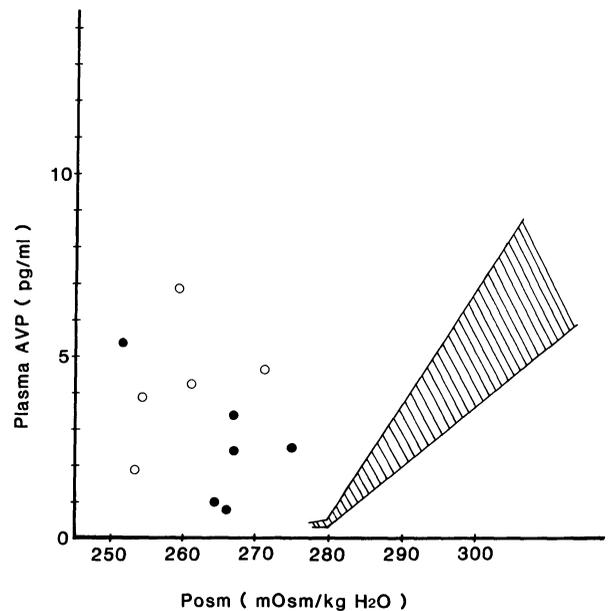


Fig. 1. Relationship between plasma osmolality and plasma AVP levels in 2 groups of elderly patients with hyponatremia at hospitalization. Closed circles (●) show the patients with SIADH. Open circles (○) show the patients with central salt-wasting syndrome. Shaded area shows the normal range.

Table 3. Changes in plasma osmolality (Posm) and plasma arginine vasopressin (AVP) levels in response to hypertonic saline infusion (5% NaCl at a rate of 0.05 ml/kg/min)

	Time (min)				
	0	30	60	90	120
Posm, mOsm/kg H ₂ O					
Elderly	289.4 ± 1.3	292.6 ± 1.6	295.6 ± 1.3	300.6 ± 1.4	302.8 ± 1.1
Young	285.0 ± 0.9	289.2 ± 3.1	292.6 ± 2.2	297.0 ± 3.1	298.2 ± 3.1
Plasma AVP, pg/ml					
Elderly	1.4 ± 0.3	2.7 ± 0.6	5.7 ± 1.3*	6.5 ± 1.8	9.6 ± 1.3
Young	1.0 ± 0.3	1.5 ± 0.4	1.9 ± 0.4	3.6 ± 0.5	6.0 ± 2.1

* $P<0.05$ vs. the young group. Values are the means ± SEM, $n=6$.

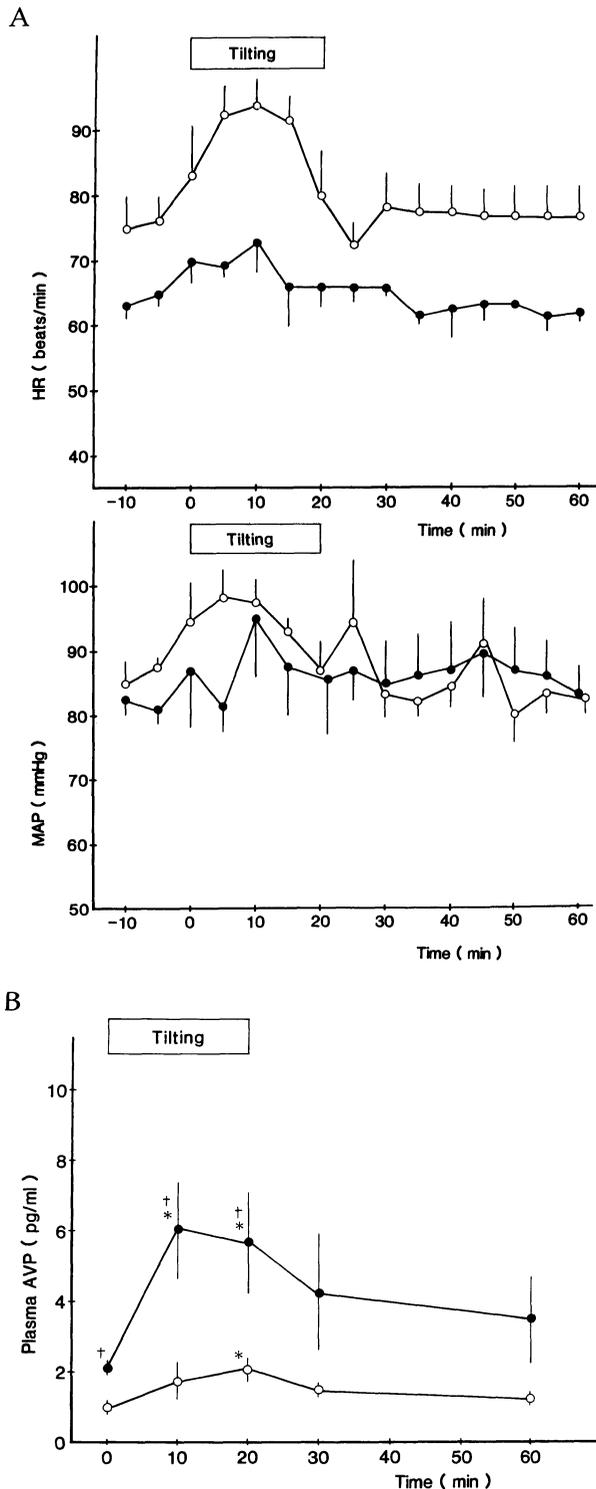


Fig. 2. Effect of 60° head-up tilt on heart rate (HR) and mean arterial pressure (MAP) (A) and plasma AVP levels (B) in young and elderly subjects. Open circles (○) show the young subjects and closed circles (●) show the elderly ones. * $P < 0.05$ vs. the value before the head-up tilt. + $P < 0.05$ vs. the respective value of the young subjects. Values are the means \pm SEM, $n = 6$.

osmolality increased comparably by 13 mOsm/kg H_2O in both the elderly and young groups of subjects, which is sufficient to stimulate osmotic release of AVP. An increase in P_{osm} caused a significant increase in plasma AVP levels in both groups of subjects. The release of AVP seemed high in the elderly subjects when compared with that in the young ones, though there was no significant difference between the two groups. The results of the tilting test are shown in Fig. 2. A twenty min head-up tilt produced significant increases in the heart rate and mean arterial pressure (MAP) in the young group of subjects. In contrast, in the elderly group there was no significant alteration in the heart rate and MAP in response to the head-up tilt. Figure 2 (B) shows plasma AVP levels. Plasma AVP levels significantly increased in response to the stimulation of the head-up tilt in both groups of subjects. However, the magnitude was significantly greater in the elderly group than in the young group. Head-up tilt caused a significant increase in PRA in both groups, and there was no difference in PRA response between the two groups (data not shown).

Therapy for Hyponatremia

Since dehydration was present in the patients with central salt-wasting syndrome, whose other manifestations were compatible with SIADH, water restriction could not be tried as an initial therapy. They were given 15–20 g/day of NaCl for 14–154 days, but serum Na levels remained low, associated with the exaggerated renal loss of Na. Of course, the patients whose serum Na levels were below 120 mEq/l were given hypertonic saline intravenously and the serum Na level was kept above at least 120 mEq/l. Secondly, fludrocortisone acetate at a dose of 0.1–0.4 mg/day was taken orally to correct hyponatremia. Within a week serum Na levels were elevated above 135 mEq/l, and serum K levels decreased to the low-normal from the high-normal value (Fig. 3). Also, urinary excretion of Na was reduced. The increase in body weight during the 3 months of observation was 2.9 ± 0.4 kg. Hematocrit levels decreased after the administration of the drug (data not shown) and indicated a $7.8 \pm 1.3\%$ decrease in circulatory blood volume during the episodes of hyponatremia. The dose of fludrocortisone ace-

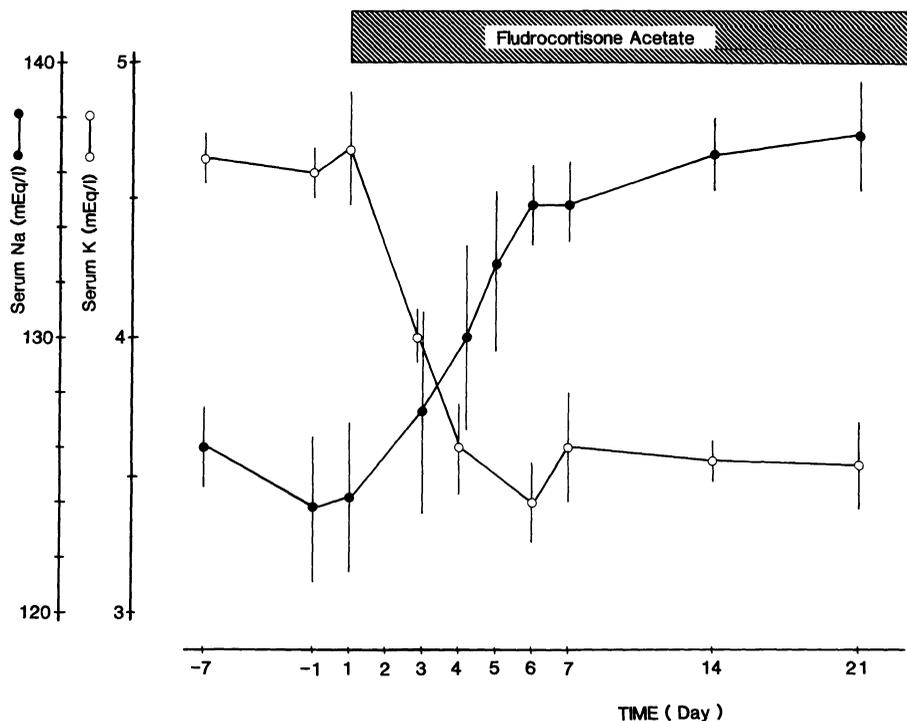


Fig. 3. Changes in serum Na and K levels after the fludrocortisone acetate therapy in five patients with central salt-wasting syndrome. The dose of fludrocortisone acetate ranged from 0.1 to 0.4 mg/day. Closed circles (●) and open circles (○) show serum Na and K levels, respectively. Values are the means \pm SEM, $n=5$.

tate was thus reduced to 0.1 mg/day in all of the 5 patients, and serum Na levels normalized. However, this therapy could not discontinue at least 6 months after the start of therapy, because hyponatremia occurred again.

The patients with SIADH restricted water intake of less than 20 ml/kg body wt. In three of 6 patients (patient no. 2, 4 and 6 shown in Table 1) serum Na levels gradually normalized in approximately 30 days. In contrast, in the other 3 patients hyponatremia was unchanged. Thereafter, fludrocortisone acetate at a dose of 0.1 mg/day was administered orally to the latter 3 patients who were not sensitive to water restriction. Urinary excretion of Na was reduced, and serum Na levels normalized in 9 days. There was no edema and hypertension throughout its therapeutic period.

Discussion

We demonstrated serious hyponatremia in 11 elderly patients with SIADH and central salt-wast-

ing syndrome. They had either hypovolemic or euvolemic hyponatremia. The volume condition was decided by the physical findings and the alteration in hematocrit during the hospitalization. We did not directly measure their circulatory blood volume.

The present study strongly shows that plasma AVP levels were not reduced despite hypoosmolality, which should suppress plasma AVP levels to undetectable levels in normal human and animals [16]. Such an elevation of plasma AVP levels, found in all the two groups of patients, depends on the following two situations. First, AVP was inappropriately secreted from the posterior pituitary in the patients with SIADH. Second, AVP release may occur in response to the decrease in circulatory blood volume in the patients with central salt-wasting syndrome. In the latter cases, an elevation of plasma AVP seemed appropriate in maintaining circulatory blood volume. However, the situation was complicated in the patients with central salt-wasting syndrome. The increased level of plasma AVP may not be merely responsible

for the alteration in circulatory distress. We consider that AVP is involved in the pathogenesis of hyponatremia *per se*. This reason will be discussed in detail below.

In a previous study [9], we demonstrated a common course of hyponatremia responsive to fludrocortisone acetate in three elderly patients after head injury. The group of patients with central salt-wasting syndrome included the three patients in the present study. Hyponatremia was associated with hypoosmolality, hypertonic urine and persistently increased urinary excretion of Na. It is unlikely that renal and adrenal functions were poor enough to have produced a massive renal loss of Na. Plasma AVP levels were relatively high despite hypoosmolality. The influence of age on AVP secretion may also be involved in the development of hyponatremia because AVP release is greater in the elderly subjects than in the young. This was also described by other investigators [17, 18]. We can mention that the reduced renal concentrating ability also contributes to the enhancement of AVP secretion from the neurohypophysis in the elderly subjects. These findings are not inconsistent with the pathological state of SIADH. As mentioned above, the physical findings include dry skin and a dry tongue at the hospitalization in four of 5 patients and fluctuation in hematocrit values and body weight suggested the presence of dehydration. Therefore, we had to distinguish these disorder from SIADH. Such a category is derived from the following reasons. There are the findings of inversely proportional changes in serum electrolytes, namely, a reduction in Na and increase in potassium and the rapid normalization of serum electrolytes in response to fludrocortisone acetate therapy [9]. Also, hyponatremia persisted for a long time because the patients could not maintain normal serum Na levels, even more 6 months after the start of fludrocortisone acetate therapy, without the administration of the drug.

Low renin activity and concomitant low levels of aldosterone were not expected in the condition of dehydration. These alterations are not infrequently found in elderly persons, whether or not they are accompanied by hyponatremia [19, 20]. DeFronzo [21] showed that salt wasting is uncommon in 81 elderly subjects who had hyporeninemic hypoaldosteronism. Since hyponatremia dramatically improved after the therapy with

fludrocortisone acetate, however, hyponatremia may have a close relation with the disorder of renin-aldosterone system. Other factors including atrial and brain natriuretic peptides can not be ruled out [22]. Elevation of plasma AVP and hypoaldosteronism appear to have been involved in the pathogenesis of hyponatremia in the patients with central salt-wasting syndrome. The increase in plasma AVP might have interrupted the compensatory mechanisms to maintain Na balance, that resulted in the increased renal loss of Na and hyponatremia. Elevation of plasma AVP seems frequent in the elderly subjects, and it is not easily mentioned that the increase in plasma AVP levels is a secondary phenomenon due to reduced circulatory blood volume. Rather, we believe that inappropriate secretion of AVP should occur independently of loss in circulatory blood volume. We know that hyponatremia is hard to occur in healthy, elderly subjects, since there are tight interactions among the central release of AVP, renal action of AVP and renal sodium handling mechanisms. The enhanced secretion of AVP may be a causative factor for initiating such a disorder as hyponatremia in patients with central salt-wasting syndrome.

We had six elderly patients with SIADH. Hyponatremia and the associated alterations were compatible with the diagnostic criteria of SIADH. Restriction of water intake less than 20 ml/kg body wt had been allowed, but in only three of 6 patients were serum Na level normalized. In the other 3 patients the signs of hyponatremia were not alleviated after the therapy. Hyponatremia remained unchanged in association with the exaggerated renal loss of Na. We decided the therapy of mineralocorticoid hormone in these 3 patients, and hyponatremia normalized in 9 days in response to fludrocortisone acetate. We could not distinguish the elderly patients with SIADH who responded to the water restriction therapy from those who did not respond to it, before the start of treatment. There was no difference in physical findings and laboratory data between the above-mentioned two groups of patients. Since AVP secretion is greater in the elderly subjects than in the young, we can not evaluate that SIADH in the elderly subjects is an equal situation to that in the non-elderly. The causes of hyponatremia may be multifactorial in the elderly patients who are diagnosed as SIADH. Taken together, hyponatremia is clinically based on SIADH, but the therapy

is not simply related to water restriction in the elderly. In other words, hyponatremia responsive to fludrocortisone acetate may be present in the elderly patients with SIADH, and SIADH in the elderly patients seems unlikely to be distinguished from the pathological state of central salt-wasting syndrome. The relative hypersecretion of AVP despite hypoosmolality may be an important trigger

for hyponatremia in the pathological state of central salt-wasting syndrome in the elderly patients, but its maintenance to keeping serum Na level normal rather seems likely to depend on renal Na handling. The criteria for SIADH in the elderly patients may have to be reevaluated, and should be considered to indicate fludrocortisone acetate therapy.

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