Aldosterone in Cerebral Salt Wasting

By John H. K. Vogel, M.D.

Although recent studies of patients with cerebral and pulmonary salt wasting have implicated "inappropriate" antidiuretic hormone secretion as the basic defect, the normality of aldosterone responsiveness has not been firmly established.1-9

This paper reports a patient with cerebral salt wasting and hyponatremia in whom balance studies suggested normal aldosterone response and inappropriate antidiuretic hormone activity.

Case Report

A 38-year-old white, single, race-car driver, was admitted to Vanderbilt University Hospital, Nashville, Tennessee, November 4, 1959, with the chief complaint of chest pain of 6 months' duration.

Four months prior to admission he was involved in an automobile accident resulting in a depressed skull fracture of the left parietal area and a subdural hematoma in the right frontal-parietal area requiring drainage with burr holes. Recovery was allegedly uneventful without neurologic deficit.

One month prior to admission he was seen at Grady Memorial Hospital in Atlanta, Georgia, with chest pain. An electrocardiogram and chest film were normal. Hyponatremia with urinary salt wasting was demonstrated, however, which subsequently responded to water restriction but not to salt loading. An intravenous pyelogram, blood nonprotein nitrogen, and urinary phenolsulfophthalein excretion were normal. Urinary 17-hydroxycorticoids were normal both resting and after stimulation with ACTH.

He admitted to moderate alcoholic intake and gave a history of acute pyelonephritis involving the right kidney 5 years prior to admission.

On physical examination the blood pressure was 108/98 mm. Hg, the pulse was 84, and respirations were 16 per minute. The skin was of good turgor and color with normal hair distribution and no abnormal pigmentation. Skull defects were palpated in the areas of the old fracture and burr holes. Except for slight weakness in the legs, the physical examination was otherwise within normal limits.

Laboratory results: Urinalysis revealed a specific gravity of 1.016, pH 5.5, negative for sugar, protein, and on microscopic. The white blood-cell count was 6,100 per mm.³, with a normal differential. The hematocrit value was 41 per cent. Fasting blood sugar was 77 mg. per 100 ml., nonprotein nitrogen 27, and cholesterol 235. Serum sodium was 127 mEq. per L., potassium 5.1, chloride 81.6, and carbon dioxide content 24. The serum total protein was 7.2 Gm. per cent, with 3.9 albumin and 3.3 globulin. The thymol turbidity was 3.0, cephalin flocculation 0 to 48 hours, and prothrombin time 72 per cent. A serologic test and L.E. preparations were negative. Serum calcium, phosphorus, and alkaline phosphatase were normal. Urinary 17-hydroxycorticoids were normal, varying from 6.3 to 19 mg. per 24 hours. The electroencephalogram was normal and an electrocardiogram was normal except for low voltage. The chest film suggested minimal pulmonary emphysema. Spine films were normal, and skull films revealed an old fracture on the left and burr holes on the right. A spirogram was normal.

The chest pain varied markedly and was unrelated to activity, position, or meals with inconsistent responses to medications and placebos. The weakness of the legs was inconsistent, did not inhibit normal activity, and was unrelated to serum sodium levels. Neurologic consultants found no evidence of residual or active disease. Psychiatric evaluation suggested a psychopathic personality.

On ad lib. water intake of 1,890 to 3,500 ml. per day and sodium intake of 90 mEq., hyponatremia with urinary sodium wasting persisted. Therefore, metabolic balance studies were instituted.

Methods

A weighed diet with a basic content of 250 ml. of water and 8.6 mEq. of sodium with constant calorie, carbohydrate, fat, and protein composition was given daily. This permitted sodium and water intake to be varied without altering the basic diet. Body weight was determined daily under standard conditions. Urine was collected in 24-hour lots from 8:00 a.m. to 8:00 a.m., and blood was drawn at 8:00 a.m. daily. Serum and urine were analyzed for sodium and potassium by flame photometer. Osmolality (mOsm/l. Kg.) of serum and urine was determined in duplicate from freezing-point depression with a Fiske osmometer. Urinary aldosterone was determined in triplicate by the double-isotope derivative assay of Kliman and Peterson.9 Normal excretion by this technic

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Averages 10 µg. per 24 hours and ranges from 5 to 19. No aldosterone values were determined on days 4, 6, 8, 9, 15, and 16.

**Results**

*Effects of high sodium and high water intake:* (Days 1-3, table 1 and fig. 1) Prior to the balance study while on ad lib. water and sodium intake, the serum sodium varied from 117 to 127 mEq. per L. and the 24-hour urine sodium excretion from 47 to 239 mEq. On the first and third days of the study the findings were similar. However, on the second day only, the patient failed to take the full water allowance with a subsequent rise in aldoster-
Table 1

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Effects of Sodium and Water Intake:

1. Oral intake: Each subject received a sodium-free diet and free water clearance with failure to lower urine osmolality below 121. No significant and free water clearance with failure to lower urine osmolality below 121. No significant
change in creatinine clearance occurred in either subject.

Three hours after the water load each subject received 50 ml of 95 per cent ethyl alcohol by mouth over a 5- to 10-minute period.

In the control subject there was a significant increase in urine flow and free water clearance 1 hour after the alcohol load, resulting in a negative water balance of 168 ml. during the 7-hour period (excluding insensible water loss). In the patient, no significant change occurred in urine flow or free water clearance, resulting in a positive water balance of 445 ml. during the 7-hour period. No significant change in creatinine clearance occurred in either subject.

**Discussion**

Cerebral disease with hyponatremia and excessive urinary sodium wasting has been reported by Peters et al., Epstein and Maceul, Epstein and Levitin, Goldberg and Handler, and Carter et al. In McCrory and Maceul's patient, a 5½-month-old girl with diffuse cerebral disease, restriction of water in relation to sodium resulted in normal serum sodium levels. The response to a water load was abnormal as manifested by a failure of urine osmolality to fall below 150. A bioassay for antidiuretic hormone while the patient was hyponatremic was markedly positive, but a control was essentially negative. With exogenous salt-retaining steroids there was an increase in body weight, but not of serum sodium.

Epstein and Levitin's patient, a 19-year-old girl with epilepsy, was similar to the above patient. There was a definite inverse relation between water intake and serum sodium, positive bioassay for antidiuretic hormone after water loading, and failure to decrease urine osmolality normally following an alcohol load. With combined sodium and water restriction, however, the urinary sodium excretion decreased to 2 mEq. per day.

The four patients studied by Goldberg and Handler were strikingly similar to the patients noted above. Their serum sodiums were
inversely proportional to water intake, and large sodium loads were ineffective in raising the serum levels unless combined with water restriction. One patient failed to change urine osmolality with alcohol.

As with our patient, one of Carter et al.'s patients developed hyponatremia following a skull fracture, and although the fracture healed completely he remained persistently hyponatremic when allowed free access to water. With either restriction of sodium to 17 mEq per day or 9-alpha-fluorohydrocortisone a positive sodium balance was attained.

The basic defect in these cases of cerebral salt wasting would appear to be the inappropriate secretion of antidiuretic hormone. However, the positive responses to salt restriction or exogenous salt-retaining steroids suggest a normal aldosterone mechanism.

A similar syndrome of salt wasting associated with bronchogenic carcinoma has been reported by Schwartz et al., and careful studies in three patients revealed hyponatremia, urine osmolality consistently higher than serum osmolality, and excessive urinary salt wasting, which was attributed to inappropriate antidiuretic hormone secretion. The serum sodium was closely related to and inversely proportional to fluid intake, with no significant response to high-sodium intake except during water restriction. All patients developed a positive sodium balance on exogenous salt-retaining steroids and after ACTH. Aldosterone determinations were low normal in the presence of hyponatremia during both low- and high-sodium intake. These results suggested normal aldosterone responsiveness.

Dossetor et al., recently reported another patient with bronchogenic carcinoma complicated by hyponatremia in whom an inverse relationship between serum sodium and water intake was noted, and thought to be a consequence of inappropriate antidiuretic hormone. As with our patient, aldosterone excretion was normal during balance periods of low sodium with excess water intake and high sodium with restricted water intake. The effect of combined low sodium and water intake was not studied, but presumably would have resulted in an increased aldosterone excretion, as occurred in our patient. Dashe and Henkin have also reported a case of inappropriate antidiuretic hormone secretion following yttrium hypophysectomy.

The role of extracellular fluid volume in the regulation of aldosterone secretion has been well documented by Bartter et al. They produced the control findings in our patient by the simultaneous administration of Pitressin and a water load to a salt-depleted subject. This resulted in a decreased aldosterone excretion, serum sodium, and osmolality but an increase in urinary sodium excretion and body weight. Similar results have been noted by Cox, Leonard, and Singer, and Leaf et al. in human subjects, and by Leaf and Mamby in dogs. Thus, it is clear that inappropriate secretion of antidiuretic hormone may be the basic abnormality in this type of excessive urinary sodium wasting with hyponatremia.

The second study period in our patient of water restriction with normal sodium intake, during which urinary sodium excretion remained high and aldosterone low, has also been produced by Bartter et al. They demonstrated that by maintenance of a normal extracellular fluid volume with a reduced fluid intake of hypertonic concentration and subsequent contraction of the intracellular space, aldosterone and sodium excretion continued unchanged.

With combined sodium and water restriction, the extracellular fluid volume will decrease and aldosterone secretion will increase in an effort to re-expand the extracellular fluid volume by the conservation of sodium, if the aldosterone mechanism is normal, and, as shown (days 8-12), this occurred in our patient.

The last phase of the study (days 13-16), stresses further the regulatory importance of the extracellular fluid volume. With a normal water intake and low sodium intake, the extracellular fluid volume increased rapidly by virtue of the abnormal level of antidiuretic hormone with a prompt decrease in aldosterone excretion and an increase in urinary sodium excretion.

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The response in the control subject to water and alcohol loads, characterized by maximum diuresis 1 hour after the respective loads is in agreement with other reports in normal subjects.16 The failure of our patient to decrease urine osmolality below 100, or to sustain any significant change in free water clearance after water and alcohol loads in the face of a normal creatinine clearance, is highly suggestive of inappropriate antidiuretic hormone secretion.3

The studies of Rubini et al.,17 suggest that the effect of ethyl alcohol is on the release or production of antidiuretic hormone in that normally a 60- to 90-minute lag period occurs before a response to the alcohol load is noted. This represents the time necessary for circulating antidiuretic hormone to be cleared. Thus, the failure of our patient and others18 to respond to alcohol loads suggests inappropriate secretion of antidiuretic hormone.

Of interest is a recent report by Grumer et al.18 on a patient with episodic inappropriate secretion of antidiuretic hormone, but no apparent underlying disease. In their patient and in our patient, the mechanism of the inappropriate secretion of antidiuretic hormone is not clear. Whether there has been a resetting of the "osmostat," or persistence of an abnormal stimulus to antidiuretic hormone secretion is not apparent.

The results in our patient suggest a normal responsiveness in aldosterone stimulation, secretion, and end-organ effectiveness in association with inappropriate antidiuretic hormone secretion.

The maintenance of a normal aldosterone mechanism suggests that the receptors regulating aldosterone-stimulating hormone may be independent of the hypothalamus. In support of this are recent studies suggesting that these receptors may be located in the kidney.19,20

Summary

A metabolic balance study in a patient with cerebral salt wasting is reported. The results suggest that a normal aldosterone mechanism was present in association with inappropriate antidiuretic hormone secretion.

Acknowledgment

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References


Richard Bright

He could not have been called a brilliant man. He made at first no great impression on those about him. But brilliancy is often ephemeral; very often brilliancy spells instability. Bright showed a steadfastness of purpose and an equanimity that are rarer and more precious than mere brilliancy. He was a simple, straightforward, kindly man, who met life with charity and tolerance and serenity; a conscientious, painstaking physician; a patient, careful, modest, scrupulous time-taking observer. He became a wise and learned man, and the fruits of his labours assure him a well-merited and honourable immortality.

Bright was buried in Bethnal Green. There is a tablet dedicated to his memory in St. James' Church in Piccadilly. The inscription ends with these words:

"He contributed to medical science many discoveries and works of great value,
And died while in the full practice of his profession after a life of warm affection

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