Hyponatremia without Inappropriate Secretion of Vasopressin in a Case of Myxedema Coma

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Abstract

A 45-year-old woman with myxedema coma due to primary hypothyroidism manifested hyponatremia, impaired water excretion, and elevated urine osmolarity as well as natriuresis suggestive of a syndrome of inappropriate antidiuretic hormone secretion. However, plasma vasopressin was undetectable or very low and plasma aldosterone levels were suppressed in the presence of hyponatremia. Subsequent replacement therapy with levothyroxine caused a rapid decline in sodium clearance which was independent of the change in glomerular filtration rate, and corrected the impaired water excretion and hyponatremia. Plasma vasopressin levels returned to the normal range after the correction of hyponatremia. Thus, the results indicate that neither vasopressin nor aldosterone plays a dominant role in the pathogenesis of the hyponatremia in this patient. It appears that thyroid hormone deficiency itself caused the derangement of tubular cell function, which resulted in the development of the impaired water excretion and hyponatremia.

Hyponatremia in hypothyroidism, which is most frequently observed in myxedema coma (Bähler et al., 1966; Sterling et al., 1966), is characterized by impaired renal water excretion and incomplete suppression of urine osmolality in the face of plasma hypo-osmolality (Bloomer et al., 1954; Discala and Kinney, 1971). Since this pathophysiological characteristic resembles that of excessive vasopressin secretion, several reports on clinical cases proposed the syndrome of inappropriate secretion of antidiuretic hormone as the cause for this disorder (Goldberg and Reivich, 1962; Chinitz and Turner, 1965; Pettinger et al., 1965; Formeister et al., 1978). However, the plasma vasopressin level was not determined in these patients. Skowsky and Kikuchi (1978) recently reported an inappropriately elevated plasma vasopressin level after acute water load in 15 of 20 hypothyroid patients. On the other hand, several investigators have denied any major role of vasopressin in the mechanism underlying this disorder. Instead, they proposed either altered renal hemodynamics (Davies et al., 1952; Hlad and Bricker, 1954; Ford et al., 1961), altered proximal and distal nephron function (Derubertis et al., 1971; Discala and Kinney, 1971; Ismail-Beigi and Edelman, 1973; Emmanouel et al., 1974; Michael et al., 1976), or relative hypoadrenocorticism (Vogt, 1960) as the cause for this disorder. Furthermore, plasma
vasopressin was suppressed in a patient with secondary hypothyroidism and hyponatremia (Macaron and Famuyiwa, 1978). Thus, the pathogenesis of hyponatremia in hypothyroidism remains highly controversial.

We report a case of myxedema coma with hyponatremia, in which plasma vasopressin levels were serially determined to elucidate the cause for hyponatremia. The results indicate a causative mechanism in which no inappropriate vasopressin secretion is involved.

**Method**

After admission, a urine catheter was inserted and both urine and blood samples were obtained at 8 hr intervals till the fifth hospital day and once a day thereafter. Sodium and potassium concentrations were determined by flame photometry. Standard formula (Tyler et al., 1968) was used for the estimation of osmolarity. Plasma vasopressin was measured using the radioimmunoassay (Shimizu and Hoshino, 1978). The assay was sensitive to 0.5 pg/ml, and the normal value was 3.1±1.2 pg/ml (mean±SD, n=40: P-Osm, 287.5±4.7 mOsm/kgH2O). Plasma aldosterone was determined by the radioimmunoassay using a commercial kit (CIS), over the normal range, 20-180 pg/ml. The serum free T4 concentration was determined by radioimmunoassay (Amerlex). The normal range of free T4 was 0.68–1.80 ng/dl.

**Case Report & Results**

The patient was a 45-year-old woman. In 1976, she had been diagnosed as having primary hypothyroidism and was prescribed 150 µg of levothyroxine a day. However, she discontinued to visit a hospital on her own a year after the diagnosis. Since then, she had suffered from increasing tiredness and cold intolerance. Ten days before admission she caught a cold and was confined to bed. Because of progressive deterioration of consciousness and abnormal behavior, she was admitted to Maruyama Memorial Hospital on Jan. 16, 1981.

On physical examination, she was totally unconscious, had a body temperature of 35 °C. Respiration was shallow and 14/min, pulse rate 42/min, and blood pressure 120/60 mmHg. Her skin was cool, scaly and pale. Her face was edematous and her tongue was enlarged. The neck vein was flat, and no thyroid tissue was palpable. Lung was clear and the left border of cardiac dullness was 2 cm beyond the mid-clavicular line. The cardiac rhythm was regular, and the sounds were decreased in intensity. No murmurs were noted. Neither the liver nor spleen was palpable. Pitting edema of moderate severity was noted on both lower extremities. The deep tendon reflexes demonstrated marked delay of the relaxation phase.

The hematocrit was 27%, and the white blood cell count 3600, with a normal differential. Urinalysis disclosed a pH of 7.0, specific gravity of 1.016, 2+ acetone, and no sugar or protein. The sediment contained a small number of red cells and leukocytes. Total serum protein was 6.9 g/dl with albumin 4.8 g/dl. The blood urea nitrogen was 11 mg/dl, total cholesterol 135 mg/dl, glutamic oxaloacetic transaminase 75 U, glutamic pyruvic transaminase 40 U, lactate dehydrogenase 918 U, and creatine phosphokinase 127 mU/ml. Serum sodium was 132 mEq/l, potassium 3.7 mEq/l, and chloride 90 mEq/l. X-ray of the chest demonstrated enlarged cardiac silhouette but no evidence of pleural or pericardial effusions or pulmonary infection. An electrocardiogram showed a sinus bradycardia with a rate of 40 and a low voltage. The determination for thyroid hormone level of the serum obtained on the first hospital day revealed T₃ less than 30 ng/dl, T₄ 0.3 µg/dl, free T₄ 0.075 ng/dl, effective thyroxine ratio 0.78, and TSH 252 µU/ml. Plasma cortisol was within the normal range at 14.8 µg/dl.

After admission, 200 mg of hydrocortisone succinate was given daily as a con-
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Fig. 1. Patient's response to levothyroxine administration.

stant infusion. Because her clinical manifestations were consistent with those of myxedema coma, she was given 250 μg of levothyroxine on the second hospital day, 100 μg and 50 μg as a bolus and 100 μg as a constant infusion for 16 hr (Fig. 1). The administration of levothyroxine was continued, but the dose was reduced to 50 μg a day on the fourth and fifth hospital day and to 25 μg a day thereafter. By this treatment, free thyroxine level rose from 0.075 ng/dl to 0.5 ng/dl at 6 hr after the beginning of levothyroxine administration and then gradually declined. In accord with the change in free thyroxine level, both temperature and pulse rate rose significantly by 2 hr after levothyroxine administration and then gradually declined. Blood pressure was maintained within the normal range except for two occasions of rapid fall after intramuscular administration of 5 mg and 2.5 mg of diazepam for her involuntary and convulsive movements. After the beginning of thyroxine administration, her consciousness was gradually restored and she became alert enough to take fluid by mouth by the sixth hospital day.

The pertinent data on her sodium and water metabolism are shown in Fig. 2. On admission, serum sodium and osmolarity were slightly lower than normal. At this stage plasma vasopressin was already undetectable, although the plasma aldosterone level was normal (9.5 pg/ml). After the infusion of 2 l of 0.45% saline solution (1 l of 0.9% saline and 1 l of 5% glucose

Fig. 2. Response to levothyroxine administration of parameters on sodium and water metabolism. S-Na indicates serum sodium; P-Osm, calculated plasma osmolarity; CNa, sodium clearance; Ccr, creatinine clearance. Open and closed bars in the lowest panel indicate daily intake and output of sodium, respectively.
solution) for the first 36 hr, both serum sodium concentration (123 mEq/l) and plasma osmolarity were markedly lowered. The plasma aldosterone concentration was also lowered to 7 pg/ml. The urine volume during that period was only 0.8 l in spite of low insensible perspiration due to severe hypometabolism. In spite of hyponatremia and hypo-osmolar plasma, inappropriately high osmolarity of the urine (552 mOsm/kg H$_2$O), high natriuresis (130 mEq/day) and high sodium clearance (1.8 ml/min) were observed. After the beginning of levothyroxine administration, the urine volume was increased, the natriuresis was markedly reduced, and serum sodium level and plasma osmolarity began to rise and finally normalized by the 7th hospital day. The fall in sodium clearance was apparently independent of the change in the glomerular filtration rate (creatinine clearance). During this recovery phase, plasma vasopressin levels were invariably undetectable or very low, and restored only after the normalization of serum sodium level.

**Discussion**

Clinical manifestations of the present patient were apparently consistent with the diagnosis of myxedema coma. Low serum sodium level and low plasma osmolarity associated with hyper-osmotic urine and high natriuresis are typical of the hyponatremia in hypothyroidism (Bloomer et al., 1954; Discala and Kinney, 1971). These pathophysiological characteristics are also compatible with those of the syndrome of inappropriate antidiuretic hormone secretion. However, plasma vasopressin levels were undetectable by the radioimmunoassay throughout her clinical course until both serum sodium level and osmolarity returned to the normal range. In addition, no significant elevation of vasopressin level occurred during the period when sodium clearance fell dramatically in response to thyroxine administration.

Because of the limited sensitivity of the vasopressin assay (0.5 pg/ml), it is difficult to demonstrate the correlation between the low plasma vasopressin level and urine osmolarity. However, as reported previously in normal volunteers under acute water load, urine osmolarity does not exceed plasma osmolarity at the plasma vasopressin level less than the sensitivity of the present assay (Shimizu and Hoshino, 1978). Contrary to this result, urine osmolarity of this patient was higher than plasma osmolarity while plasma vasopressin was undetectable. This indicates that abnormal vasopressin secretion was not responsible for the present disorder, and that vasopressin secretion was actually suppressed due to extracellular fluid expansion. Alternatively, the hypersensitivity to vasopressin of renal tubules may cause a similar abnormality. However, the renal resistance to circulating vasopressin has been reported in some hypothyroid patients (Skowsky and Kikuchi, 1978). Thus, it seems that neither the abnormal vasopressin secretion nor the hypersensitivity of renal tubules to vasopressin is responsible for the defect in water and sodium metabolism of this patient.

Aldosterone also may not be responsible for hyponatremia, since the plasma aldosterone level was initially within the normal range and then adequately suppressed with the fall of the serum sodium level and plasma osmolarity. Aldosterone secretion appeared to be inhibited by the extracellular volume expansion induced by the impaired water excretion and re-hydration, and secondary aldosteronism did not exist in spite of hyponatremia. Likewise, glucocorticoid deficiency does not appear to be the causative factor, because the plasma glucocorticoid level was normal on the first hospital day and hyponatremia progressed in spite of the administration of a sufficient amount of glucocorticoid.
Earlier studies have proposed either a change in renal hemodynamics (Davies et al., 1952; Hlad and Bricker, 1954; Ford et al., 1961) or altered renal tubular cell function irrespective of vasopressin action (Derubertis et al., 1971; Discala and Kinney, 1971; Ismail-Beigi and Edelman, 1973; Emmanouel et al., 1974; Michael et al., 1976) as the cause of the impaired water excretion and hyponatremia in hypothyroidism. In this respect, it is of interest that thyroid hormone administration rapidly lowered sodium clearance and corrected both hyponatremia and the impaired water excretion without changes in plasma vasopressin level. Furthermore, the decline in sodium clearance was independent of the change in creatinine clearance. Therefore, contrary to the earlier reports (Davies et al., 1952; Hland and Bricker, 1954; Ford et al., 1961), at least the changes in glomerular filtration rate and probably renal plasma flow do not account for the defect in this patient. Taking all these together, it is concluded that vasopressin was not responsible for the hyponatremia in the present case. It seems that thyroid hormone deficiency itself might have caused the change in tubular cell function which resulted in the impaired water excretion and hyponatremia. However, the possibility still remains that the cause of this disorder is heterogeneous, as Skowsky and Kikuchi’s data indicate (1978). Further studies are definitely needed to arrive at a conclusion on the pathophysiological role of vasopressin in this disorder.

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References


