Chronic Hypernatremia Associated with Inflammation of the Neurohypophysis

TOSHIKAZU SAITO, SHO YOSHIDA, KIKU NAKAO, AND RIICHIRO TAKANASHI

The Third Department of Internal Medicine, and The Department of Pathology, Faculty of Medicine, University of Tokyo, Hongo, Tokyo, Japan

ABSTRACT. A sustained hypernatremia associated with chronic nonspecific inflammatory change of the neurohypophysis has not hitherto been described. A case of a 66-yr-old woman who showed hypernatremia and clinical manifestations of dehydration of 1 month's duration is reported. She had hypodipsia and impairment of urine concentration. Hypernatremia and dehydration were successfully treated with Pitressin Tannate. Autopsy findings revealed a marked fibrosis and infiltration of lymphocytes and plasma cells confined to the neurohypophysis. It was concluded that the hypernatremia was induced by hypodipsia and the deficiency of release of antidiuretic hormone from the neurohypophysis was due to chronic inflammatory change. (J Clin Endocr 31: 391, 1970)

IN NORMAL man the concentration of serum sodium is maintained within a relatively narrow range (1). The regulation of concentration is much influenced by the release of antidiuretic hormone (ADH) from the neurohypophysis and water intake in response to the sensation of thirst. Chronic and sustained hypernatremia in adults is a rare disorder and has been reported occasionally in patients having central nervous system lesions (2). A chronic inflammatory lesion localized in the neurohypophysis, however, has not been described as an etiology of chronic hypernatremia.

The present report documents a case of a 66-yr-old woman with hypernatremia of one month's duration which was corrected by the injection of Pitressin Tannate. The autopsy findings revealed a neurohypophysis with marked fibrosis and infiltration of lymphocytes and plasma cells. These results suggest the nonspecific chronic inflammatory process was responsible for the clinical course of ADH deficiency and are quite unique in the morphology of this organ.

Received April 23, 1970.
Partly supported by a grant from the NIH, USPHS (AM-11278).

Case Report

A 66-yr-old Japanese woman was admitted to the Third Department of Medicine, University of Tokyo, in January 1967 because of delirium and marked dehydration. In her past history the patient had been in good health except that she was sterile and underwent an operation for subcutaneous implantation of a bovine pituitary in 1951. Six yr prior to admission she began to have severe attacks of bronchial asthma and was treated with adrenocorticoids, which had been irregularly continued until the present admission. She began to show a moon face, obesity and glycosuria, and the diagnosis of mild diabetes mellitus was made in 1963. After the summer of 1966 she sometimes complained of easy fatigability and dryness of the mouth, which had been getting worse. Ten days prior to admission she became delirious and subsequently dehydrated.

On admission she was 78 kg in body weight and 154 cm in body length, with a moon face and buffalo hump. She had nausea, vomiting and marked deterioration of menation and memory. The sensation of thirst was not complained of although her skin and oral mucosa were severely dry, it being necessary to moisten her tongue for speaking. The blood pressure was 142/105, pulse rate 88/min. Laboratory data showed a hemoglobin of 15.5 g/100 ml, hematocrit 45%, a white cell count of 7200 per cm with a normal differential count. The urinalysis revealed a specific gravity of 1007, the absence of albumin or glucose, and an unremarkable sediment. The other blood values showed a sodium of 162 mEq/l, potassium 3.6
mEq/l, chloride 119 mEq/l, blood urea 10 mg/100 ml, creatinine 1.3 mg/100 ml and total cholesterol 262 mg/100 ml. The fasting blood sugar was 178 mg/100 ml and values of 329 and 275 were obtained 2 and 3 hr, respectively, after the oral administration of 100 g of glucose. The fasting blood sugar ranged from 96 to 186 mg/100 ml and urine sugar from 3.5 to 9.8 g/day during her hospital days. Roentgenograms of the skull, chest and gastrointestinal tract showed no remarkable findings. High voltage 4 or 5 cycles/sec slow waves were seen in all leads of the electroencephalogram and no localized abnormalities were observed. The adrenal function was studied by rapid ACTH test (3). Plasma cortisol, measured by the method of Rudd et al. (4), was 0.7 µg/100 ml (normal 7.0–17.0 µg/100 ml) before and 6.0 µg/100 ml (normal 10.9–32.3 µg/100 ml) 30 min after intravenous injection of β-th-ACTH. The Tr resins uptake was 37.4% (normal 25–38%). The phenolsulfophthalein test showed 10% excretion of injected dye in 15 min and 47.5% in 2 hr. Creatinine clearance calculated from 24-hr urinary excretion of endogenous creatinine was 40 ml/min (normal 85–125 ml/min). After 16 hr of water deprivation the concentration of the serum sodium rose from 161 to 170 mEq/l and the urinary specific gravity from 1010 to 1014. The concentration of ADH in plasma measured by the method of Yoshida et al. (5) was 4.7 µU/ml after this water deprivation (normal 3.4–9.0 µU/ml) (5). Intramuscular injection of 5 U of aqueous Pitressin resulted in a decrease in urinary excretion from 5.0 to 0.75 ml/min and elevation of urinary osmolality from 172 to 451 mOsm/l 120 min after injection.

The course of serum level and urinary excretion of sodium, urine volume and water intake is shown in Fig. 1. The concentration of serum sodium ranged from 159 to 170 mEq/l, serum chloride from 117 to 126 mEq/l and 24-hr urine volume from 1050 to 4000 ml/day, with a specific gravity from 1003 to 1012 until February 22, when treatment with hydrochlorothiazide and then with Pitressin Tannate was started. The patient was given 15–25 mEq of sodium orally or intravenously and excreted 12–76 mEq of sodium in urine each day during this period. From 10 to 20 mg of prednisolone was daily administered intravenously or orally. She was infused with 1000–1500 ml of 5% glucose solution and encouraged to take considerable fluid. The increase in fluid intake, however, resulted in an increase in urinary volume and no improvement was observed in the concentration of serum sodium and the clinical findings of dehydration. From February 23 to March 6 she was daily given 75 mg of hydrochlorothiazide, which caused a decrease in the serum sodium level to 143 mEq/l and an increase in urinary excretion of sodium, while no improvement was obtained in the dryness of skin and oral mucosa. From March 2, treatment with Pitressin Tannate was started and the response to this therapy was striking. In addition to the marked decrease in urinary volume and elevation of the specific gravity of urine, an improvement was observed in the serum level, the clinical symptoms of dehydration and in psychiatric aspects such as deterioration and amnesia. BUN fell, ranging from 5 to 7 mg/100 ml. In addition, the electroencephalogram showed the disappearance of the high voltage slow waves which were remarkable at her admission. She was treated with 1.5 U of Pitressin Tannate every other day and discharged from our clinic in April in good condition. Two months after her discharge, however, she had a severe attack of bronchial asthma associated with dyspnea and cyanosis and expired 10 hr after the onset of the attack.

**Autopsy and Histological Findings**

Autopsy examination of the gastrointestinal tract, liver, spleen and kidneys revealed no remarkable changes in these organs. In the thyroid gland there was no noteworthy change, except for slight fibrosis and colloid adenomatosis. The lungs showed marked overdistention and obstruction of the bronchus and bronchioles with tenacious mucus. The infiltration of numerous eosinophilic leukocytes and thickening of the basement membrane were observed in bronchioles. The pancreas showed an atrophic change, slight fibrosis and few β-granules in the islets, and this finding was compatible with the diagnosis of diabetes mellitus. The adrenal cortex was atrophic, with concomitant depletion of lipid substance. No remarkable lesion was found in the tissue adjacent to the hypophysis such as the bony sella turcica, optic chiasma and basilar surface of the brain. The adenohypophysis showed a vacuolar degeneration of basophilic cells which seemed to be caused by pro...
Prolonged administration of adrenocortical steroids.

The histological examination of the neurohypophysis revealed a diffuse fibrosis and a marked infiltration of lymphocytes and plasma cells. The infiltration of these cells was extensive, with partial formation of lymph follicles (Fig. 2, 3). Polymorphonuclear cell infiltration was not observed. A similar change was also observed in the neural stalk to a lesser degree. The pituitary was swollen and the interstitial space was widened and the neurohypophysis was edematous as a whole. The supraoptic nuclei examined by Nissl’s stain revealed slight degenerative changes which were not remarkable in the caudate and mamillar nuclei. The macro- and microscopic examination of the brain showed no changes such as bleeding, softening, neoplasma or inflammation in this organ.

**Discussion**

In previous reports chronic hypernatremia has occasionally been associated with lesions in the central nervous system (2),
Fig. 2. Neurohypophysis showing marked infiltration of the round cells (R), formation of lymph follicles (L) and fibrosis (F) (hematoxylin and eosin stain, $\times 60$).

Fig. 3. Neurohypophysis at a higher magnification showing infiltration of the round cells (R) and normal part (N) (hematoxylin and eosin stain, $\times 150$).
especially the hypothalamus (6). Although the pathogenesis of this disorder is not yet fully clarified, several authors have emphasized that the coexistence of the hypodipsia and elevation of the threshold or deficiency of ADH release due to a disturbance of the hypothalamo-neurohypophysial system is essential for this disorder (6, 7). In the present case the existence of the disorder of the neurohypophysis was suggested from several clinical symptoms: hypernatremia, dehydration and marked water diuresis following the injection of fluid without any concomitant improvement of hypernatremia. Moreover, she showed a significantly depressed ability to concentrate urine following a water deprivation test. The urine was concentrated adequately, meanwhile, by the injection of Pitressin Tannate and a striking lowering of the serum sodium level followed this. The concentration of plasma ADH was low normal compared with that in a 16-hour water deprivation test in a normal subject (5). The osmotic stimulus accelerating ADH release, however, would be much stronger in the present case than in a normal subject and it follows that the titer would be low in consideration of her plasma hypertonicity. These findings seem to confirm the presence of neurohypophysial insufficiency.

Several authors have recently reported asymptomatic or essential hypernatremia associated with postoperative craniopharyngioma (7), pinealoma (8), Hand-Schüller-Christian disease (9), or of unknown etiology (10). Mahoney and Goodman (7) have characterized the clinical manifestations of this syndrome as hypernatremia without polyuria and polydipsia which may be due to the elevation of the “osmotic threshold” for ADH release and decreased or absent thirst sensation. The symptoms of the present case were quite consistent with these characteristics and a high reset threshold for ADH release might be suggested. However, similar to the case of Kastin et al. (8), the fluctuation of serum sodium concentration was much wider than normal (1) in the present case, as was illustrated by the water deprivation test. Consequently, it may be more probable that the disturbance of the ADH releasing system in the present case was not a mere leveling up of the osmotic threshold, but was a deficiency of the ADH releasing ability in response to the osmotic stimulus, incomplete or partial diabetes insipidus (14).

The striking histological findings observed in the neurohypophysis and concomitant changes of the supraoptic nuclei seem to be unequivocally compatible with these considerations. A number of pathological findings of patients with diabetes insipidus have been reported in the hypothalamo-neurohypophysial system (11). In the present case marked fibrosis and infiltration of lymphocytes and plasma cells suggested the presence of a long-standing nonspecific inflammatory change that could be termed “posterior hypophysitis.” Lymphocytic infiltrations in the hypophysis were reported to be found in 10 (12) to 43.3% (13) of normal subjects. The location of the infiltration, however, is in most cases near the pars intermedia and rare in the pars nervosa or neural stalk (13). In none of these cases were other findings obtained that suggested inflammatory changes such as the concomitant infiltration of plasma cells or marked fibrosis. As to the etiology of diabetes insipidus, Thomas (14) showed a case associated with “nonspecific inflammatory reaction” in his table of a series of 65 patients with diabetes insipidus. Except for this description, the finding of a neurohypophysis similar to the present case has not previously been reported in a subject with or without clinical manifestations. The etiology of these pathological findings is obscure, but inflammation due to bacterial infection seems to be improbable since neither the infiltration of polymorphonuclear cells in the neurohypophysis nor inflammatory change in adjacent tissues was observed. It may be
speculated by analogy that there had been some immunological process similar to anterior hypophysitis (15, 16). This hypothesis seems to be interesting especially in consideration of the implantation of the bovine hypophysis in her past history.

In addition to ADH deficiency the disturbance of the thirst mechanism should be a coexistent factor for a sustained hypernatremia. On the patient’s admission the thirst sensation was apparently suppressed. She was stuporous and disoriented in her mental state and she took little fluid notwithstanding encouragement to take more. The improvement of her mental disorder and the change of the electroencephalogram after correction of the hypernatremia suggested that her mental disorder including the hypodipsia was due to dehydration itself, at least in part. Thirst and fluid intake, meanwhile, were obviously depressed even after consciousness improved and the presence of a relatively confined disturbance of the thirst center was postulated. Although the autopsy findings have not completely clarified the disturbance, the changes observed in the supraoptic nuclei and neurohypophysial stalk were not incompatible with it.

Acknowledgment

The authors are indebted to Dr. Yasuo Tokoro, The Department of Pathology, Faculty of Medicine, University of Tokyo, and Dr. Masanori Uno, The Third Department of Internal Medicine, Faculty of Medicine, University of Tokyo, for their valuable comments on the interpretation of the histological findings.

References

1. Elkiton, J. R., and T. S. Danowski, The Body Fluids, Williams & Wilkins Co., Baltimore, 1955, p. 120.