Case Report

Syndrome of Inappropriate Secretion of Antidiuretic Hormone (SIADH) in a Patient with Multiple Sclerosis

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Association of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) with multiple sclerosis (MG) is very rare, although many other disorder of the nervous system have been reported to be associated with this syndrome; there is only one case report in the literature. We describe here a patient with the syndrome associated with MS. A 62-year-old woman had a variety of neurologic symptoms, where clinical course was typical of MS. Transient episodes of hyponatremia and disturbance of consciousness occurred repeatedly with deterioration of MS. The concentration of antidiuretic hormone (ADH) was high whereas the plasma osmolality was low in the presence of concentrated urine, during the episodes of hyponatremia. Urinary Na excretions exceeded 20 mEq/day. Computed tomography and magnetic resonance imaging revealed lesions in the brain, especially in the periventricular region. The hypothalamus and pituitary appeared normal by these imaging methods. Since the periventricular region surrounds and may be functionally connected to the hypothalamus which plays the central role in the regulation of ADH secretion, it was concluded that association of SIADH and MS in this patient was not coincidental, and that demyelinating processes in the periventricular region exerted an abnormal influence on ADH secretion resulting in SIADH. Contribution of other mechanisms as increased intrathoracic pressure, however, could not be excluded completely.

Key words: The syndrome of inappropriate secretion of antidiuretic hormone (SIADH), Multiple sclerosis.

Since the first description of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in a patient with bronchogenic carcinoma by Schwartz and Bartter in 1957 (1), many disorders including diseases of nervous system have been reported to be associated with this syndrome. On the other hand, SIADH is very rare in patients with multiple sclerosis (MS), a demyelinating disease characterized by multiple foci in the central nervous system and optic nerve: to our knowledge, there is only one case report of SIADH associated with MS in the literature (2) except for the patient on whom we previously reported in a preliminary form (3).

We describe here the patient including the subsequent course; the syndrome occurred repeatedly with exacerbations of MS. Our conclusion is that the association was not coincidental.

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Case report

A 62-year-old woman was admitted for the first time to our hospital in July, 1984. Sensory disturbance, dysuria and weakness of the lower extremities had developed since 1981. She lost the vision in her left eye in February, 1983. On admission, slight increases in protein (54 mg/dl) and IgG (4.3 mg/dl) in cerebrospinal fluid (CSF), and an oligoclonal band of IgG on an electrophoresis were noted. A diagnosis of MS was made according to the diagnostic criteria for MS (4). Treatment with prednisolone was started and she was discharged in August, 1984.

She was again admitted comatose to our hospital on 8 April, 1985. Before this admission her visual and sensory disturbances had exacerbated and then

remitted. Weakness of the upper limbs had developed immediately before admission. Neurologic examination revealed flaccid paraparesis of the upper limbs with a positive Babinski sign on the right. A slight degree of pretibial pitting edema was noted. The skin was not dry. The blood pressure was 122/92 mmHg, and the pulse rate 68. Laboratory data on admission are summarized in Table 1. IgG in CSF was increased. Serum Na was low (121 mEq/l) and plasma osmotic pressure was decreased markedly (239 mOsm/Kg) in the presence of concentrated urine (452 mOsm/Kg). Sodium in the urine was more than 35 mEq/day. The plasma ADH level was markedly elevated (> 35 pg/ml). The

urea nitrogen was 5.0 mg/dl, and the creatinine 0.3 mg/dl. The uric acid was 1.1 mg/dl. The creatinine clearance rate was 67 ml/min. Data of adrenal functions were normal as shown in Table 1. Plasma prolactin was 17 ng/ml. On the basis of these findings a diagnosis of SIADH in addition to an exacerbation of MS was made. Disturbance of consciousness was considered mainly due to water intoxication. Therefore, restriction in daily water intake up to 1 L and administration of prednisolone again were instituted. Three days after admission, serum Na was increased to 136 mEq/l, and she became alert. Plasma ADH was also decreased to 3.3 pg/ml. Plasma osmotic pressure returned to 280 mOsm/Kg. Paresis of the upper limbs gradually decreased, and she was discharged on 3 May, 1985. The course of this patient until the discharge was reported previously (3).

Six months after discharge, paralysis of the left upper limb appeared suddenly. A low density area in the posterior portion of the right internal capsule was seen on computed tomography (CT), which was interpreted to suggest an acute lesion of MS, although the possibility of cerebrovascular disease could not be completely denied.

She was admitted for the third time on 8 January, 1987. She had complained of neck pain, sense of oppression in the chest and generalized muscle weakness. On admission, the blood pressure was 127/85 mmHg, and the pulse rate 94. No finding suggestive of ischemic heart disease was obtained. Although for skin was slightly dry, there were no other signs of dehydration. A marked degree of tetraparesis was noted. Sensation was bilaterally diminished below the level of T4. Deep tendon reflexes were hyperactive. Prednisolone, maintained at 20 mg/day, was increased to 30 mg/day. She had hypoxia and hypercapnea, and was profoundly dyspneic with diminished movements of the chest. Oxygen was administered transnasally. On the second hospital day, she became semicomatose. Laboratory data at that time are shown in Table 2. Serum Na was 121 mEq/l. The urea nitrogen was 11.0 mg/dl, and the creatinine 0.5 mg/dl. The uric acid was 1.5 mg/dl. The creatinine clearance rate was 64 ml/min. Plasma osmotic pressure was 239 mOsm/Kg. Urinary Na excretion constantly exceeded 20 mEq/day. Plasma ADH was 27.6

Table 1. Laboratory data during the second admission

Laboratory data during the second admission

Urinary chemistry

Na	44 mEq/day
K	49.2 mEq/day
Cl	53 mEq/day
Urine Osm	452 mOsm/Kg

Blood count

RBC	$411 \times 10^4/\text{mm}^3$
Hb	12.6 g/dl
Ht	35.3%
WBC	$6100/\text{mm}^3$
Platelet	$21.2 \times 10^4/\text{mm}^3$

Blood chemistry

Total protein	5.7 g/dl
A/G	1.78
Glucose	146 mg/dl
BUN	5.0 mg/dl
Creatinine	0.3 mg/dl
Uric acid	1.1 mg/dl
Na	115 mEq/L
K	4.5 mEq/L
Cl	86 mEq/L
Plasma Osm	249 mOsm/Kg

Endocrinological test

ADH	> 35 pg/ml
PRA	0.35 ng/ml/hr
Aldosterone	166.8 pg/ml
Cortisol	29.0 μ g/dl
Urinary 17-OHCS	5.0 mg/day
Urinary 17-KS	1.6 mg/day

Table 2. Laboratory data during the third admission

Laboratory data during the third admission	
Urinalysis	
Glucose	(—)
Protein	(—)
Sediment	N P
Blood count	
RBC	401×10 ⁴ /mm ³
Hb	12.7 g/dl
Ht	33.9%
WBC	3700/mm ²
Platelet	24.3×10 ⁴ /mm ³
Blood chemistry	
Total protein	6.7 g/dl
Albumin	4.0 g/dl
GOT	21 IU
GPT	13 IU
Glucose	136 mg/dl
BUN	11.0 mg/dl
Creatinine	0.5 mg/dl
Uric acid	1.5 mg/dl
Na	121 mEq/L
K	3.4 mEq/L
Cl	84 mEq/L
Plasma Osm	239 mOsm/Kg
Urinary chemistry	
Na	116.3 mEq/day
K	35.9 mEq/day
Cl	125.5 mEq/day
Urine Osm	389 mOsm/Kg
Endocrinological test	
ADH	27.6 pg/ml
PRA	0.39 ng/ml/hr
Aldosterone	69.8 pg/ml
Cortisol	31.7 μg/dl
Urinary 17-OHCS	16.9 mg/day
Urinary 17-KS	5.7 mg/day

pg/ml. Plasma prolactin was 19 ng/ml. Urinary 17-OHCS and 17-KS while taking prednisolone were 16.9 and 5.7 mg/day, respectively. A diagnosis of SIADH was made again. Low density areas in the periventricular region around the both anterior horns of the lateral ventricle, and that extending from the posterior portion of the right basal ganglion to the centrum semiovale with brain

Fig. 1. Head computed tomography taken during the third admission shows low density areas in the periventricular region around both of the anterior horn of the lateral ventricle (↓), and that extending from the posterior portion of the right basal ganglion to the centrum semiovale (↓↓) with dilatation of the ventricles.

atrophy were recognized on cranial CT (Fig. 1). Magnetic resonance imaging (MRI) revealed findings similar to those identified by CT. In addition, there were marked atrophic changes in the midbrain, medulla and spinal cord. These findings on CT and MRI were interpreted to suggest new lesions of MS. However, no abnormality was found in the hypothalamus or pituitary by these imaging methods. Dyspnea was considered due to paresis of respiratory muscles. Because she was still dyspneic despite oxygen inhalation, she was placed on a respirator. Hypertonic saline was administered intravenously and daily water intake was restricted up to 600 ml. The dose of prednisolone was further increased to 40 mg/day. Four days after admission, serum Na was normal and she became completely alert. On 29 January, she resumed spontaneous breathing and the respirator was removed.

DISCUSSION

In this case a diagnosis of MS was made according to the criteria proposed by Posner et al. (4). The clinical course was typical of MS with ex-

acerbation and remission of neurological symptoms. There were also episodes of transient hyponatremia associated with deterioration of neurologic manifestations. Since plasma ADH was inappropriately elevated in the presence of decreased plasma osmotic pressure, a diagnosis of SIADH was also made in each episode. Other criteria for a diagnosis of SIADH (5, 6) were fulfilled in our case, except for pretibial pitting edema noted on the second admission. Usually edema has not been observed in SIADH because the total amount of water retained rarely exceeds 5 L, an amount not sufficient to produce edema, along with the continued excretion of Na. It may be that normal or increased intravascular volume seen in most patients with SIADH counteracts against ADH by keeping normal or increased glomerular filtration (7). PRA was not elevated, but rather suppressed and the uric acid was also low in our patient. These data are compatible with SIADH, suggesting the presence of increased effective intravascular volume in this patient. It might be a cause of edema that glomerular filtration rate might have not increased in proportion to increased effective intravascular volume, though her renal function was almost normal. Other factor(s) also might have contributed to edema. In certain edematous conditions a reduction in effective intravascular volume results in impaired water diuresis and hyponatremia. However, it seemed unlikely that these mechanisms had operated in this patient based on the low PRA and uric acid levels. Thus, localized edema of a slight degree may not be sufficient to preclude the diagnosis of SIADH. Moreover, good responses to water restriction which was undertaken in combination with administration of NaCl were typical of SIADH.

Generalized muscle weakness observed in the third admission was evidently not a manifestation of hyponatremia. Although serum K was slightly decreased at that period, it seemed unlikely that disturbance of serum electrolytes underlay the symptoms. It was rather a neurological manifestation of MS, which responded later to prednisolone.

The secretion of ADH is normally regulated by plasma osmotic pressure and blood volume. When concentrations of ADH in the blood are inappropriately elevated relative to plasma osmotic pressure in the absence of blood volume depletion by per-

turbation of the relationship between ADH secretion and plasma osmotic pressure, SIADH will result. Several mechanisms, other than aberrant production of ADH as observed in some cases of neoplasms such as lung cancers, for the development of the syndrome have been postulated. These are (1) increased stimulation of ADH release, (2) removal of the inhibition against ADH release and (3) leakage of the stored ADH from neuroendocrine neurons. In CNS disorders, which associate SIADH most frequently next to malignant neoplasms, one of the three mechanisms also may be applicable. The hypothalamus and posterior pituitary play the central role in the regulation of ADH secretion. Although it is not well defined, the periventricular region, which surrounds the hypothalamus, may have functional communication with it. Afferent pathways, one of which relay non-osmotic signals and the other noradrenergic terminating on the paraventricular nucleus, to ADH-secreting cells may traverse at least a part of these region. Lesions or dysfunction in these regions, therefore, could be responsible for SIADH.

Perloth et al. reported a case of acute intermittent porphyria associated with SIADH in which degeneration and destruction of the supraoptic nucleus were verified (8). Stein et al. also described a patient with porphyria who was found at autopsy to have atrophy and gliosis of the supraoptic nucleus with vacuolated neurosecretory cells in the tuberohypophyseal tract (9). It is likely that in these cases organic lesions in the hypothalamus, especially those of the supraoptic nucleus, caused SIADH, probably due to leakage of the stored ADH.

To our knowledge, the association of the syndrome with MS is very rare. Apple et al. reported a patient with MS associated with SIADH who also had galactorrhea with elevated serum prolactin levels (2). They postulated that leakage of ADH caused by demyelinating brain damage might be responsible for SIADH. Although galactorrhea and elevated prolactin suggest a hypothalamic lesion, it seems, however, difficult to locate precisely the responsible region in the brain, because ADH-secreting neuron is unmyelinated and no pathological examination was performed in their study. Taking into a case of MS reported by Kamalian et al. in which, although not associated with SIADH, demyelinating lesions

in the hypothalamus was found (10) into consideration, it is very likely that demyelinating lesions in the hypothalamus might cause SIADH in Apple's case.

In our case SIADH occurred simultaneously twice with exacerbations of MS. Lesions in the brain, especially in the periventricular region, were identified by cranial CT and MRI performed at the third admission, whereas the hypothalamus and pituitary appeared normal. Although normal images on cranial CT and MRI do not preclude minor changes in size, it was, therefore, less likely that lesions in the hypothalamus and pituitary caused the syndrome. It was rather very likely that lesions in the periventricular region exerted an abnormal influence on the hypothalamus and posterior pituitary in our case. The lesions might have damaged the inhibitory nerve tract to the hypothalamus, resulting in inappropriately high plasma ADH levels. Alternatively, the stimulatory nerve tract might have been nonspecifically activated by demyelinating processes. Lastly, the possibility of ADH leakage due to demyelinating changes in the hypothalamus, which might be too small in size to be detected by MRI and CT, could not be completely ruled out in our case. In our case plasma prolactin was normal in the period of hyponatremia, which is rather incompatible with the last possibility.

During the period of the third admission, this patient was placed on a respirator because of dyspnea and hypercapnea owing to weakness of respiratory muscles. This might have been the cause of SIADH in the third admission. It is well known that hypercapnea itself enhances ADH secretion by stimulating the respiratory center in the medulla, and that hypotension due to vasodilatation caused by accumulated carbon dioxide in the blood also enhances ADH secretion. Hypoxia also enhances ADH secretion (11). Since hypercapnea and hypoxia were, however, relieved immediately by artificial respiration in this patient, this did not seem to play an important etiologic role in our case. The possibility, rather, can not be excluded that the increased intrathoracic pressure, which were probably present due to positive end expiratory pressure, might have contributed in part to increased ADH secretion being mediated by decreased vagal activity as observed in SIADH associated with bronchial

asthma and pneumonia (12, 13).

In summary, although the association of SIADH and MS is rare, MS can be causally related to this syndrome. Although other mechanisms, e.g. increased intrathoracic pressure and hypercapnea, also might have operated during the second episode of SIADH, demyelinating lesions in the brain, especially in the periventricular region, might be responsible for the development of this syndrome in our case, whatever the mechanism.

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