Syndrome of Inappropriate Secretion of Antidiuretic Hormone Associated with Multiple Sclerosis

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A 63-year-old man who developed episodes of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) twice in the course of multiple sclerosis (MS) is reported. SIADH in this patient occurred only during the administration of antibiotics (sulbactam/cefoperazone, SBT/CPZ). At autopsy, demyelinating lesions in the optic nerves, cervical and thoracic spinal cord, and areas adjacent to the lateral ventricles were observed. Destruction and loss of neuronal cells were found in the supraoptic nuclei. Lymphocytic infiltration was observed in the area adjacent to the supraoptic nuclei. Destruction and swelling of axons and reactive astrocytic gliosis were observed in the hypothalamus. SIADH associated with MS is rare and the histological findings in such a case have not yet been reported. It is suggested that the development of SIADH in MS may be related to the damage in the supraoptic nuclei of the hypothalamus.

(Key words: hyponatremia, supraoptic nucleus lesion, antibiotics (sulbactam/cefoperazone))

Introduction

Since the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) was first described by Bartter and Schwartz (1), many cases of SIADH in conjunction with malignant tumors, diseases of the central nervous system, lung diseases, or the use of various drugs have been reported. SIADH occurs rarely in multiple sclerosis (MS); only two cases have been reported (2, 3). The histological examination of the hypothalamus, and especially of the supraoptic nuclei, which seems to be related to the secretion of antidiuretic hormone (ADH), have not previously been described in MS. We report a case of MS presenting SIADH and describe the lesions of the supraoptic nuclei found at autopsy.

Case Report

A 59-year-old man was admitted to our hospital in October 1985, because of bilateral weakness of the lower extremities, sensory loss below the T2 level, dysuria, and decreasing visual acuity. He had suffered from bouts of remission and exacerbation of postoptic neuritis since January 1985. Brain computed tomography (CT) and spinal cord magnetic resonance imaging (MRI) showed no abnormal findings. The concentrations of total protein, IgG and myelin basic protein (MBP) in cerebrospinal fluid (CSF) were increased and oligoclonal band IgG was detected. His symptoms and signs were reduced with steroid therapy.

He was readmitted in September 1986, because of weakness of the lower and upper extremities and total blindness. His condition gradually worsened in spite of steroid therapy. In February 1987, difficulty in breathing due to paresis of the respiratory muscles appeared. His respiratory problem required the use of a respirator. On neurological examination, consciousness was clear, orientation was good, and there was no abnormality in cranial nerves, except for the loss of bilateral visual acuity and severe atrophy of the optic nerves. Severe weakness with hyperreflexia of the upper limbs and complete flaccid paraplegia with a pathologic reflex of the lower limbs were found. Complete sensory loss below the C2 level was observed. He also had difficulty in urination.

In June 1988, drowsiness associated with hyponatremia appeared (Fig. 1, Table 1). Neurological examination
Table 1. Laboratory Data on the First Episode of Hyponatremia

<table>
<thead>
<tr>
<th>Blood chemistry</th>
<th>Na 106 mEq/l, K 4.7 mEq/l, Cl 79 mEq/l, Cr 0.3 mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN 10.3 mg/dl, UA 1.8 mg/dl, TP 6.9 g/dl</td>
<td></td>
</tr>
<tr>
<td>BS 125 mg/dl, Ccr 61.2 ml/min</td>
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<tr>
<td>Plasma Osm. 237 mOsm/kg H2O</td>
<td></td>
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<tr>
<td>Blood count</td>
<td>RBC 340 x 10^4/l, Ht 30.3%, Hb 10.6 g/dl</td>
</tr>
<tr>
<td>WBC 10,500/µl</td>
<td></td>
</tr>
<tr>
<td>Pit 28.2 x 10^4/µl</td>
<td></td>
</tr>
<tr>
<td>Urine chemistry</td>
<td>Na 38 mEq/l (42 mEq/day), NAG 5.3 U/l</td>
</tr>
<tr>
<td>ft-microglobulin 591 µg/dl</td>
<td></td>
</tr>
<tr>
<td>ADH 1.8 pg/ml</td>
<td></td>
</tr>
<tr>
<td>Aldosterone &lt;2.0 ng/dl</td>
<td></td>
</tr>
<tr>
<td>Plasma renin activity 0.47 ng/ml/h</td>
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</tbody>
</table>

revealed no significant change except for the disturbance of consciousness. The serum sodium level recovered rapidly and his consciousness became clear after discontinuing the administered antibiotic (sulbactam/cefoperazone, SBT/CPZ), replacing the sodium loss and restricting fluids to 1,000 ml/day. Serum sodium levels became stable at between 130 and 140 mEq/l, although fluid restriction was discontinued. When the same antibiotic (SBT/CPZ) was readministered, hyponatremia reappeared (Fig. 1, Table 2), and again the treatment was discontinuation of the antibiotic and restriction of fluids. In October 1988, the patient died of pneumonia. The duration of the clinical course was three years and ten months.

The autopsy findings (Central Nervous System)

Autopsy was performed four and a half hours after death. The brain weighed 1,410 g. There was little cerebral atrophy but slight enlargement of the lateral ventricle was found. Optic nerves and the upper thoracic spinal cord were remarkably atrophic. The left hemisphere and spinal cord were fixed by paraffin and stained with hematoxylin-eosin (HE), Klüver-Barrera (KB), Bodian's stain and glial fibrillary acidic protein (GFAP). In the cerebral hemisphere, small demyelinating plaques were found in the adjacent white matter of the anterior horn of lateral ventricle. Demyelinating plaques were observed in the whole area of the bilateral optic nerves and the lower cervical and upper thoracic spinal cord. Many macrophages with fat vacuoles, focal lymphocytic infiltration, axonal degeneration and pronounced astrocytic gliosis were found in these areas.

The coronal section of the hypothalamus between the optic chiasma and the infundibulum is shown in Fig. 2. At higher magnification, pronounced lymphocytic infiltration was observed in the area of the infundibulum and in the area adjacent to supraoptic nuclei. Loss of neuronal cells was also observed in the portion of the supraoptic nuclei near the infundibulum (Fig. 3A). Degeneration of neuronal cells was found in the portion of the supraoptic nuclei far from the infundibulum, whereas there were no findings of lymphocytic infiltration (Fig. 3B). Degeneration and loss of neuronal cells was clearly demonstrated in comparison with a normal control (Fig. 3). In the paraventricular nuclei, there was only slight degeneration of neuronal cells and lymphocytic

Fig. 2. Coronal section of the hypothalamus between the optic chiasma and the infundibulum. (hematoxylin-eosin stain, ×6.6) 3V, third ventricle; CB, cerebral base; PVN, paraventricular nuclei; SON, supraoptic nuclei.
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Discussion

The present patient was diagnosed to have MS, according to the criteria proposed by Poser et al (4). He had repeated episodes of remission and exacerbation of the postoptic neuritis and transverse myelopathy, increased IgG, and a positive oligoclonal band in CSF. The findings at autopsy showed multiple demyelinating lesions at areas adjacent to the lateral ventricle, the optic nerves, and the spinal cord.

When hyponatremia and a decrease in plasma osmolality were observed, there was a corresponding increase in urine osmolarity and urinary sodium excretion. Plasma ADH level was 1.8 pg/ml when plasma osmolarity was 258 mOsm/kg·H₂O, indicating an inappropriately high level of ADH. Renal glomerular and tubular function were not impaired. Thyroid and pituitary-adrenal functions were normal and plasma prolactin levels were within normal limits. Plasma renin activity and plasma aldosterone levels were low. The patient did not show any evidence of dehydration, heart failure, or liver cirrhosis. These findings suggested that the hyponatremia in this patient was induced by SIADH.

In the present patient, malignant tumors and lung diseases were not found. Although this patient had been using a respirator for 18 months, his state of breathing was good and stable when he had SIADH. Drugs which commonly cause SIADH were not administered at all (5–7). However, SIADH occurred during the administration of SBT/CPZ. It is suggested that SIADH in this patient might have been induced by MS alone or by the effect of SBT/CPZ on MS.

The mechanisms of the increase in ADH secretion associated with MS have not been well defined. Perlroth et al (8) described severe damage to the supraoptic nuclei in a case of acute intermittent porphyria associated with SIADH. As the area of inflammation in the hypothalamic-hypophyseal tracts in their case did not extend far enough to directly involve the supraoptic nuclei, they postulated that damage of these tracts might cause the retrograde degeneration of neuronal cells. Also, leakage of ADH caused by that damage might be responsible for SIADH. Apple et al (2), who reported a case of SIADH associated with MS, suspected the presence of hypothalamic lesions caused by MS and postulated similar mechanisms, since the increase in serum prolactin level, SIADH and exacerbation of neurological symptoms were observed at the same time. In contrast, Ishikawa et al (3) reported a case with lesions in the periventricular region identified by brain CT and MRI, without any evidence of damage to the hypothalamus or pituitary. Therefore, they postulated that SIADH is caused by damage of the inhibitory nerve tract to the hypothalamus.

The histopathological examination in the present patient demonstrated supraoptic nucleus lesions similar to those described in the report of Perlroth et al (8). The loss of neuronal cells in the present case might have been infiltration. Destruction and swelling of axons and reactive astrocytic gliosis were also found in the hypothalamus. There were no abnormal findings in either anterior or posterior pituitary lobes.

Fig. 3. A) Higher magnification of the supraoptic nuclei indicated by the arrow in the Fig. 2. (hematoxylin-eosin stain, ×50) B) Higher magnification of the supraoptic nuclei indicated by the arrowhead in the Fig. 2. (hematoxylin-eosin stain, ×50) C) Normal control supraoptic nuclei (hematoxylin-eosin stain, ×50).
caused by the same mechanisms occurring in cases of acute intermittent porphyria. It is likely that damage of the supraoptic nuclei could be related to the appearance of SIADH associated with MS.

Hypothalamic lesions associated with MS have been reported in several cases. Bignami et al (9) reported the observation of large demyelinating plaques throughout the entire hypothalamus in a patient with MS who had acute depression, organic mental disturbance, and hypothermia. Kamalian et al (10) reported the presence of demyelinating plaques in the lateral hypothalamus in an MS patient with rapid weight loss and numbness of the arms and legs. These reports demonstrate that demyelinating lesions associated with MS can extend to the hypothalamus and induce hypothalamic symptoms and signs.

However, it is not clear why hyponatremia appeared only when SBT/CPZ was administered in the present patient case and why the serum sodium level was stable within normal limits after the discontinuation of fluid restriction. It is unlikely that the degeneration of neuronal cells in the supraoptic nuclei was caused solely by the antibiotics. Thus, we cannot exclude the possibility that in addition to the basis of hypothalamic lesions by MS, SBT/CPZ might have contributed to the secretion of ADH or to the action of ADH in renal collecting tubules (5–7).

In summary, we report the first autopsied case of SIADH associated with MS. The lesions in the supraoptic nuclei may have been responsible for the SIADH.

References