Simultaneous Occurrence of SIADH, Secondary Hypogonadism and Alopecia Universalis in a Woman with IDDM

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Abstract. Syndrome of inappropriate secretion of antidiuretic hormone (SIADH), hypothalamic hypogonadism and alopecia universalis occurred in a 31-year-old female with insulin-dependent diabetes mellitus (IDDM). Despite various clinical investigations and careful observation for 20 months, the cause and pathogenesis of SIADH and hypothalamic hypogonadism were not elucidated. The complex of these disorders had not been described. The presence of IDDM and alopecia universalis, in which an autoimmune process has been assumed to be involved, is interesting in considering the pathogenesis of the SIADH and hypothalamic hypogonadism.

Key words: Autoimmune endocrinopathy, SIADH, Hypogonadism, IDDM, Alopecia universalis.

SYNDROME of inappropriate secretion of antidiuretic hormone (SIADH) is recognized as an important cause of hypotonic hyponatremia. It can be seen in a wide variety of clinical states such as neuropsychiatric disorders, malignancy, pulmonary disease and the use of certain drugs, and usually the pathogenetic basis in each case is clarified clinically. In this paper, a case of SIADH and hypothalamic hypogonadism of unknown cause associated with alopecia universalis occurring in a patient with IDDM is reported. The complex of these changes had not been described. Although the case had revealed no circulating autoantibody and could not be classified as any type of autoimmune polyglandular syndrome, the association with IDDM and alopecia universalis appears to give a clue to the pathogenesis of the apparently idiopathic SIADH and hypothalamic hypogonadism [1–3].

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Case

A 31-year-old female was admitted for diagnostic investigation of hyponatremia, amenorrhea and alopecia universalis on July 20, 1989.

The patient was healthy until ten months before, when she was hospitalized because of thirst, excessive urination and lethargy. A diagnosis of insulin dependent diabetes mellitus was established based on laboratory tests which disclosed hyperglycemia, ketoacidosis and insulin depletion, although no islet cell antibodies (ICA) or islet cell surface antibodies (ICSA) were detected. A diffuse goiter (each 3 × 3 cm) was noted. Insulin therapy was immediately begun, and the honeymoon period came after six weeks. She returned to the outpatient clinic for observation on 6 U/day of NPH insulin.

Three months before readmission, she noticed that she had not menstruated and that a diffuse thinning of the hair over the entire scalp, axilla and pubis developed rapidly. Moreover, hyponatremia (129 mEq/L) was noticed, although she appeared to be in good health mentally and
physically. She was readmitted to the hospital for further examination. She had never been pregnant and neither past history nor family history was contributory.

Her height was 159 cm, and weight 43 kg. The body temperature was 36.6°C, the pulse 60, the blood pressure 100/60 mmHg. On physical examination, she appeared healthy and euvoletic. Loss of hair was found on the head, axilla, and pubis. A diffuse goiter, rubbery and symmetrical, was noted again. Physical examination was otherwise unremarkable.

Urinalysis was normal. The hematocrit was 41 percent; the white-cell count was 4100 with a normal hemogram. The erythrocyte sedimentation rate was 13 mm per hour. Fasting blood glucose was 82 mg/dl, and hemoglobin A1 6.8 percent. Blood urea nitrogen was 11 mg/dl, creatinine 0.7 mg/dl, uric acid 2.0 mg/dl, and the glomerular filtration rate 103 ml/min. Sodium was 124 mEq/l, potassium 4.3 mEq/l, chloride 90 mEq/l, calcium 9.5 mg/dl, phosphate 4.3 mg/dl and plasma osmolality (Posm) was 256 mOsm/kg, and urine osmolality (Uosm) was 674 mOsm/kg. Urinary excretion of sodium, potassium and chloride were 178, 54 and 169 mEq/day, respectively. Anti-nuclear antibodies, anti-microsomal antibodies, anti-thyroglobulin antibodies and antipituitary antibodies reacting against plasma membrane of AtT20 and GH3 or cytoplasma of rat pituitary cells (Biomedical Laboratories, Kawagoe, Saitama) were all negative. X-rays of the chest and the brain imaging including computed tomography and magnetic resonance imaging (MRI) did not show any abnormalities.

The basal endocrine status is summarized in Table 1. The secretory reserve of the anterior pituitary was tested by combined i.v. injection of regular insulin (0.1 U/kg), TRH (500 µg) and LH-RH (100 µg) and the results are shown in Table 2. Each pituitary hormone showed a normal response. After oral administration of 100 mg clomiphene a day for 5 days, the peak of plasma LH level was delayed and low and the plasma FSH levels were essentially unchanged (Fig. 1).

A water load test was performed to verify the defects in water excretion (Fig. 2). An oral water load of 20 ml per kilogram of body weight was given over a period of 15 min, and urine was collected hourly for the next 5 h while she was

<table>
<thead>
<tr>
<th>Blood</th>
<th>Progesterone</th>
<th>Estradiol</th>
<th>Testosterone</th>
</tr>
</thead>
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<tr>
<td>ADH</td>
<td>0.6 pg/ml</td>
<td>&lt;0.2 ng/ml</td>
<td>69.1 pg/ml</td>
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<tr>
<td>Posm</td>
<td>248 mOsm/kg</td>
<td></td>
<td></td>
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<tr>
<td>renin</td>
<td>0.5 ng/ml/h</td>
<td></td>
<td>0.4 ng/ml</td>
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<tr>
<td>aldosterone</td>
<td>150 pg/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSH</td>
<td>1.0 µU/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F-T4</td>
<td>1.8 pg/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>reverse T3</td>
<td>1.25 ng/dl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTH</td>
<td>35 pg/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cortisol</td>
<td>13.9 mg/dl</td>
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</tr>
<tr>
<td>LH</td>
<td>3.8 mIU/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSH</td>
<td>11 mIU/ml</td>
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<thead>
<tr>
<th>Table 1. Endocrine data on readmission</th>
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</table>

**Table 2.** Anterior pituitary responses to combined i.v. injection of regular insulin (0.1 U/kg), TRH (500 µg) and LH-RH (100 µg)

<table>
<thead>
<tr>
<th>(min)</th>
<th>ACTH (pg/ml)</th>
<th>cortisol (µg/dl)</th>
<th>GH (ng/ml)</th>
<th>TSH (µU/ml)</th>
<th>prolactin (ng/ml)</th>
<th>LH (mIU/ml)</th>
<th>FSH (mIU/ml)</th>
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<tbody>
<tr>
<td>0</td>
<td>35</td>
<td>10.9</td>
<td>1.8</td>
<td>0.9</td>
<td>7.7</td>
<td>3.8</td>
<td>11</td>
</tr>
<tr>
<td>30</td>
<td>24</td>
<td>10.9</td>
<td>2.3</td>
<td>10.3</td>
<td>7.1</td>
<td>66.9</td>
<td>22</td>
</tr>
<tr>
<td>60</td>
<td>25</td>
<td>11.8</td>
<td>1.4</td>
<td>9.9</td>
<td>56</td>
<td>55.5</td>
<td>24</td>
</tr>
<tr>
<td>90</td>
<td>39</td>
<td>11.8</td>
<td>8.0</td>
<td>7.9</td>
<td>56</td>
<td>50.5</td>
<td>25</td>
</tr>
<tr>
<td>120</td>
<td>29</td>
<td>16.6</td>
<td>2.8</td>
<td>6.3</td>
<td>40</td>
<td>44</td>
<td>30</td>
</tr>
</tbody>
</table>

Underlines denote each peak value.

Plasma glucose levels after insulin loading test at 0, 30, 60, 90 and 120 min are 155, 89, 55, 54 and 67 mg/dl, respectively.

![Fig. 1](image1.png)  
**Fig. 1.** Plasma LH and FSH response to oral administration of 100 mg clomiphene a day for 5 days.
Water load 800 ml

ADH (pg/ml) 0.6

Fig. 2. The effects of an oral water load of 20 ml per kilogram of body weight on plasma ADH, Posm, Uosm and urinary volume in the patient.

Fig. 3. The relation of plasma ADH to concurrent plasma osmolality during the basal state, water load test and hypertonic saline infusion test. The shaded area represents the range of normal.

She was treated with water restriction (less than 1000 ml per day) and high sodium intake. She could maintain plasma sodium above 125 mEq/l. Menstruation occurred following estrogen therapy and she was discharged. During 20 months of follow up, plasma sodium concentrations fluctuated between 120 and 140 mEq/l, but she continues to do well and is now asymptomatic. Clinical investigations including MRI of the brain performed six months after discharge have shown no evidence of any underlying disease. Although the dose of insulin required to control DM was increased gradually, no further deterioration of endocrine function was noticed.

Discussion

The patient described herein had hypotonic hyponatremia, urine osmolality inappropriately high for the low plasma osmolality, excessive natriuresis, absence of edema-forming states or volume depletion and normal cardiac, hepatic, renal and adrenal function. She had goiter of unknown etiology, and in thyroid function tests, pituitary secretion of TSH was not impaired but the serum concentration of free T3 was decreased while that of reverse T3 was inappropriately high. This condition is frequently referred to as the euthyroid sick syndrome, the cause of which was
uncertain in this patient. Euthyroid sick syndrome itself does not cause hyponatremia, although the latter is frequently accompanied by the former. As is evident from the water loading test, the patient had impaired excretion of the loaded water (excreting less than 20 percent in 5 h) and failed to dilute the urine to hypotonic levels. In response to further reduction of plasma osmolality, ADH had remained detectable in the plasma. These findings indicated that the cause of hyponatremia developed in the patient was due to an inappropriate secretion of ADH.

Dynamic studies of ADH secretion in patients with SIADH have shown that it is a heterogeneous disorder which encompasses at least four distinct types of osmoregulatory defect and that no correlation can be made between these patterns and the underlying cause of the SIADH [4]. The patient released ADH at low plasma osmolality and the plasma ADH level did not increase as the plasma osmolality rose, which indicated that the pattern of ADH secretion in the patient did not correspond to any of four types and that osmotic regulation was entirely lost. Evaluation of the functional state of volume-sensitive receptor for ADH release in this patient seems difficult because destruction of the osmoreceptor causes a marked decrease in ADH response to change in water balance, even though the volume receptor was completely intact [5].

The patient also exhibited secondary amenorrhea simultaneously with SIADH. The LH and FSH response to LHRH were normal but their responses to clomiphene (100 mg per day for 5 days) were absent. These results indicated an impaired hypothalamic response to interruption of the negative feedback effect of estrogen [6]. Based on the association of SIADH and hypothalamic hypogonadism, a hypothalamic lesion was suspected, but imaging studies with CT scans and MRI showed no abnormalities. The chronic and stable process having affected only limited hormones over a long period (20 months) makes the possibility of a tumor or vascular abnormality unlikely. As ectopic ADH production or other factors such as drugs, pulmonary diseases and neuropsychiatric disorders seem very unlikely judging from circumstantial evidence, a diagnosis of idiopathic SIADH was made.

SIADH is said to occur in certain patients without any associated conditions [4, 7]. Such cases are very rare and are not always considered to be idiopathic, because underlying psychiatric disease or other medical problems are sometimes present [8]. Moreover careful observation may reveal the cause of SIADH later. Indeed Martinez-Maldonado identified a lung malignancy in a patient with idiopathic SIADH 6 months after initial presentation [9]. Therefore, careful and repeated monitoring for the presence of an underlying disease is essential, although our patient is still diagnosed as idiopathic SIADH after 20 months of follow up.

The representative causes of SIADH, hypothalamic hypogonadism, alopecia universalis and IDDM which occurred in the patient can not be specified but, when taken together, such a common mechanism as autoimmune derangement emerges as possible pathogenic mechanism. There are multiple combinations among presumed autoimmune diseases of endocrine organs, including the adrenals, endocrine pancreas, thyroid, parathyroids, ovaries, testes and adrenohypophysis [10, 11]. In addition, these endocrinopathies are frequently associated with other disorders of tissue-specific autoimmunity, notably pernicious anemia and alopecia [12]. A hypothalamic disorder is also not exceptional because central diabetes insipidus has been reported to be associated with other well-established autoimmune disorders, especially autoimmune thyroid disease, IDDM, pernicious anemia, alopecia totalis and mucocutaneous candidiasis [13]. Scherbaum and his colleagues found that one-third of their patients with idiopathic central diabetes insipidus had antibodies acting against cytoplasm of arginine-vasopressin secreting cell, employing the indirect immunofluorescent test on unfixed or acetone-fixed sections [14]. These findings indicate that the hypothalamus is not spared by the generalized autoimmune process and SIADH and hypothalamic hypogonadism may also be an integral part of systemic autoimmune disorders. While the exact mechanism is not known, the target of autoimmune process causing SIADH may be at the level of osmoreceptor rather than the neuron secreting ADH. The absence of autoantibodies in this patient does not exclude the possibility of autoimmune disease, because the association between the disease and the presence of organ-specific autoantibodies has not been well established except for the chronic thyroiditis or IDDM [15]. Even in IDDM, ICA and ICSA may be
present only transiently and are not detected in 20–30% of newly diagnosed patients [15, 16].

In conclusion, a case has been described in which SIADH, hypothalamic hypogonadism and alopecia universalis developed ten months after the onset of IDDM. This is a very rare case because, despite various clinical investigations and careful observation for 20 months, the cause and pathogenesis of SIADH and hypothalamic hypogonadism were not revealed. Moreover the associations of IDDM and alopecia universalis suggest that an autoimmune process is involved in their pathogenesis.

References