Isolated Adrenocorticotropic Deficiency Associated with Anti-Pituitary Antibodies, Pituitary Cyst, Sphenoidal Cyst and Pineal Tumor

KAZUMI NOTSU, NOBUYUKI OKA, MOTOI SOHMIYA,
TOSHIAKI SATO, SEICHI ANDO*, KOZO MORITAKE*,
KEN-ICHI INADA**, YOSHIYUKI OSAMURA**,
AND YUZURO KATO
First Division, Department of Medicine and *Department of Neurosurgery,
Shiman Medical University, Izumo 693, and **Department of Pathology,
Tokai University School of Medicine, Isehara 259-11, Japan

Abstract. This paper reports a rare case of isolated ACTH deficiency associated with anti-pituitary antibodies, pituitary cyst, sphenoidal cyst and pineal tumor. A 68-year-old man consulted our clinic for general fatigue. Laboratory data showed low plasma adrenocorticotropic hormone (ACTH) and cortisol levels with blunted responses to insulin-induced hypoglycemia and corticotrophin releasing factor (CRF). Urinary 17-OHCS was low but responded to ACTH-Z administration. No other pituitary functions were impaired. Antibodies to the cytoplasm of rat pituitary and the surface of GH3 cells were detected in the serum. The magnetic resonance imaging (MRI) showed a high signal intensity mass in the anterior pituitary and in the sphenoidal sinus in both T1 and T2 weighted images as well as a low signal intensity mass in a T1 weighted image of the pineal region. Transsphenoidal surgery was performed to resect the mass in the sphenoid sinus and in the pituitary. Pathological studies showed a benign cyst in the sphenoid sinus, and fibrous degeneration and decreased basophils in the pituitary. No infiltrative mononuclear cells were detected in the pituitary. Immunohistochemical studies revealed a decrease in the number of ACTH-producing cells in the pituitary. The patient was well maintained by glucocorticoid replacement without any growth of a possibly benign pineal tumor.

Key words: Isolated ACTH deficiency, Anti-pituitary antibodies, Sphenoidal cyst, Pineal tumor

(Endocrine Journal 41: 631–637, 1994)

ISOLATED adrenocorticotropin (ACTH) deficiency was first described by Steinberg and colleagues [1]. Accumulated evidence indicates clinical characteristics due to heterogeneous causes [2] and frequent association with other autoimmune endocrine disorders [3]. Lymphocytic hypophysitis and selective absence of corticotrope are a common accompaniment [4, 5]. Description of positive anticotiotrope antibodies in the serum suggest that most occurrences are due to an autoimmune process [6, 7]. The defect is probably at the pituitary levels because there is no ACTH secretory response to corticotrophin releasing factor (CRF) [8].

Case Report

A 68-year-old man complained of general fatigue and loss of appetite since 1984. He consulted several clinics in which mild anemia (Hb 102 g/L; normal 138–170 g/L), low sodium (Na 127 mEq/L; normal 136–145 mEq/L) and diffuse slow wave changes in the electroencephalograph (EEG) were

Received: February 21, 1994
Accepted: July 12, 1994
Correspondence to: Dr. Kazumi NOTSU, Third Division, Department of Medicine, Shiman Prefectural Central Hospital, 116 Imaichi-cho, Izumo 693, Japan
detected. He had an episode of transient blindness in 1988. In 1990, he was admitted to the urological department in our university hospital for the treatment of prostatic hypertrophy, and he proved to have low levels of plasma glucose and cortisol. He was referred to our division for further endocrinological examination. He had never been treated with steroid hormones before admission.

Physical examination revealed that his height and weight were 160.6 cm and 47.8 kg, respectively. The body temperature was 36.0°C, pulse rate 60/min, and blood pressure 150/80 mmHg. The axillary and pubic hair was intact and no abnormal pigmentation was observed. Goiter was not palpable. The chest was normal except for presystolic murmurs of grade 1/6. No abdominal mass was palpable. Neurological examination was normal.

General laboratory data showed mild anemia (Hb 99 g/L), an increase in eosinophilic leucocytes (832×10^6/L) and low serum sodium (134 mEq/L). Fasting plasma glucose was 4.2 mmol/L.

Endocrinological examination revealed low plasma ACTH (1.54–1.76 pmol/L) and cortisol (less than 27.6 mmol/L). Intravenous injection of actrapid insulin (0.05 U/kg BW) failed to raise plasma ACTH and cortisol in spite of a significant decrease in plasma glucose. Neither ACTH nor cortisol responded to CRF (100 µg), which was either injected iv as a bolus or infused for 120 min. Plasma ACTH and cortisol were not increased by combined iv injection of CRF (100 µg) with arginine-vasopressin (AVP, 0.3 U) (Fig. 1). Urinary 17-OHCS was low but increased from 1.4 µmol/day to 34.5 µmol/day following i.m. administration of ACTH-Z (1 mg) for three consecutive days.

Plasma triiodothyronine (T3), thyroxine (T4) and free T4 levels were normal. Antithyroid antibodies were negative, but basal plasma TSH was slightly increased (10.0 mU/L) and showed an exaggerated increase after iv injection of TRH (500 µg). Basal plasma prolactin (PRL) was slightly increased (19 µg/L) and responsive to TRH administration. Basal plasma growth hormone (GH) levels and responses to insulin-induced hypoglycemia and iv injection of GH-releasing factor (GRF 100 µg) were normal. Plasma LH and FSH showed a delayed increase after LH-RH (100 µg, iv) (Fig. 2).

Both cytospot antibodies were measured by enzyme immunoassay method with [125I]TSH labeled. Anti-pituitary measured by the method of Stock. 125I were suspensions containing...
Methods and Results

Both cytoplasmic and cell surface anti-pituitary antibodies in the serum were examined as follows. Anti-pituitary cytoplasmic antibodies (PCCA) were measured by the indirect peroxidase-labeled antibody method with rat anterior pituitary as the substrate. The patient's serum inactivated and absorbed by acetone powder of rat liver was mounted on cryostat sections of rat anterior pituitary fixed in paraffin, and incubated for 30 min at 37°C. The mounted serum was washed out and peroxidase-labeled IgG was added as the second antibody. Anti-pituitary cell surface antibodies (PCSA) were measured by the indirect immunofluorescence technique with GH3 cells as the substrate by the method of Sugiura and colleagues [7]. GH3 cells were suspended in Hank's balanced salt solution containing 4% BSA (Hank's BSS). The GH3 cells (50,000/100 µl) and 50 µl of the patient's serum inactivated and absorbed by acetone powder of rat liver were incubated in Hank's BSS (950 µl) for 30 min at 4°C. The cells were washed with Hank's BSS and further incubated with FITC labeled anti-human IgG as the second antibody for 30 min at 4°C. Both PCCA and PCSA were positive in this patient (Fig. 3).

Magnetic resonance imaging (MRI) revealed a high signal intensity mass in the anterior portion of the pituitary and in the sphenoid sinus, and a low signal intensity mass in the pineal region in the T1 weighted image (Fig. 4 upper panel). All of these three masses showed high signal intensity in the T2 weighted image in MRI. The cytology of cerebral spinal fluid (CSF) was negative for malignant cells. Transsphenoidal surgery was carried out to resect the clear mass in the sphenoid sinus and in the anterior pituitary. Histological examination with hematoxylin and eosin staining revealed

---

Fig. 3. Anti-pituitary cytoplasmic antibodies (PCCA, ×400, left) and anti-pituitary cell surface antibodies (PCSA, ×200, right) in the serum of patient with isolated ACTH deficiency.
a benign cystic mass coated with membrane tissue in the sphenoid sinus. An abnormal tumor was not detected in the pituitary. The pituitary was enriched with fluid component and fibrous connective tissue. Basophilic cells were considerably decreased (Fig. 5). Infiltration of mononuclear cells did not occur in the specimen of the pituitary. Immunohistochemical examination performed with the peroxidase-labeled antibody method as previously described [9] failed to demonstrate ACTH-producing cells in the anterior pituitary tissue of the patient, whereas many ACTH-containing cells were detected in the pituitary tissue obtained from a control subject who died from congestive heart failure (Fig. 6).

After replacement with glucocorticoid (20 mg/day), the clinical course of the patient was quite good and no complaint was received. Both basal plasma TSH and PRL levels (3.5 mU/L and 42 μg/L), and their peak values after TRH loading (42.0 mU/L and 43.6 μg/L) were improved. Basal plasma LH and FSH were 4.0 IU/L and 5.8 IU/L, respectively, and normal peak values were obtained.

Fig. 4. The magnetic resonance image (MRI) of a patient with isolated ACTH deficiency. The T1 weighted sagittal view images before and after replacement with glucocorticoid (upper and lower) are shown, indicating a high signal intensity mass in the anterior portion of the pituitary, and in the sphenoid sinus as well as a low signal intensity mass with a clear margin in the pineal region (upper). The high signal intensity mass in the sphenoid sinus disappeared after transsphenoidal surgery and the pineal region did not change for two years (lower panel).

Fig. 5. Hematoxilin and eosin staining of the anterior pituitary (×400). The loss of basophilic cells and fibrous degeneration are shown. There was no infiltration of mononuclear cells.
at 30 min after stimulation with LH-RH. The size and character of the abnormal mass in the pineal region was not changed for two years and was considered clinically as a benign tumor (Fig. 4, lower panel).

Discussion

Isolated ACTH deficiency is rare disease but more than 200 cases have been described since 1954, but there have been few reports on pathological evaluation of the pituitary in patients with isolated ACTH deficiency, as shown in Table 1. Odell and colleagues first reported that ACTH content was decreased in the pituitary of a patient [10]. Further studies revealed a decreased number of basophilic cells in the anterior pituitary [4, 5, 11, 12]. We also found in the present study that ACTH-producing cells were not detectable in the biopsy specimens of the pituitary. These findings suggest that the defect is at the pituitary level.

It was reported that infiltrations of mononuclear cells into the pituitary of two patients with isolated ACTH deficiency [4, 5] suggested in the involvement of immunological disorders. Anti-pituitary antibodies were detectable in some patients with ACTH deficiency [3, 7], suggesting that autoimmune mechanisms play a role in damage to ACTH-producing cells. In the present case, we first demonstrated two different kinds of anti-pituitary antibodies (PCCA and PCSA), but mononuclear cell infiltration was not seen. The specificity to ACTH-producing cells in these autoantibodies was still unclear, but a discrepancy between positive tissue-specific antibodies in the serum and infiltrative mononuclear cells in the tissue was previously reported in patients with insulin-dependent diabetes mellitus (IDDM) which is one of the autoimmune disorders [13]. Most

Fig. 6. Immunohistochemical staining of ACTH-producing cells in the anterior pituitary of a control subject who died without endocrinological disorders (left, ×200) and biopsy specimen of the pituitary in a patient with isolated ACTH deficiency (right, ×50). ACTH-producing cells were easily detected in the control pituitary tissue but not in the biopsy specimen of the pituitary in this patient.
Table 1. Pathological and immunological characteristics in six reported cases with isolated ACTH deficiency

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Sex</th>
<th>Decreased Basophil</th>
<th>Fibrosis</th>
<th>Mononuclear Cells Infiltration</th>
<th>Anti-Pituitary Antibody</th>
<th>Author [Ref. No.]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>58</td>
<td>F</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>n.e.</td>
<td>Odell [10]</td>
</tr>
<tr>
<td>2.</td>
<td>49</td>
<td>M</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>n.e.</td>
<td>Perkoff [11]</td>
</tr>
<tr>
<td>3.</td>
<td>31</td>
<td>F</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>n.e.</td>
<td>Richtsmeier [4]</td>
</tr>
<tr>
<td>4.</td>
<td>72</td>
<td>F</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>PCcA(+)</td>
<td>Matsuo [12]</td>
</tr>
<tr>
<td>5.</td>
<td>32</td>
<td>F</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>PCcA(-)</td>
<td>Jensen [5]</td>
</tr>
<tr>
<td>6.</td>
<td>68</td>
<td>M</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>PCcA(+)</td>
<td>Present Case</td>
</tr>
</tbody>
</table>

n.e., not examined; PCcA, anti-pituitary cytoplasmic antibodies; PCsA, anti-pituitary cell surface antibodies.

patients with newly diagnosed IDDM had positive islet cell antibodies (ICA) in the serum [14, 15], but infiltrative mononuclear cells were shown in some ICA-positive cases [14]. A time-dependent decrease in mononuclear cells in the pancreatic islets of patients with IDDM was also suggested [13, 16]. We also found that fibrous connective tissues were increased in the pituitary in the present case, which is on the same line as a previous report [5]. The fibrous degeneration may indicate the final stage in the destruction of the tissue by the autoimmune process.

On the other hand, there is a paper which suggest that human fetal tissue is the best source of antigen for the detection of pituitary autoantibodies [17]. It may be necessary to measure pituitary autoantibodies by the same different methods in order to confirm our previous conclusion.

There were only a few reports on MRI findings in patients with isolated ACTH deficiency. It was reported that some patients were associated with empty sella [18]. Lymphocytic adenohypophysitis is symmetrically enlarged without any significant change in signal intensity. In the present case, a high signal intensity mass was demonstrated in the antero-lateral portion of the pituitary in both T1 and T2 weighted images, suggesting cystic lesions containing mucoid. The cystic wall was not clearly demonstrated in the biopsy specimen of the pituitary, and fibrous degeneration was strongly suggested. A similar cyst was found in the sphenoid sinus of this patient.

It is noted that the patient also had a low signal intensity mass in the pineal region. This finding suggests that the pineal tumor contained lipid or CSF. No aqueductal obstruction, Parinaud's syndrome or any other endocrinological manifestations was found. Pineal tumors may be classified into two groups: tumors of germ cell origin and tumors of pineal cell origin [19]. The former are of two major subtypes: germinomas and teratomas. The tumor in the present case has not been histologically examined yet, but it is apparently different from germinomas on the basis of age, prognosis and the cytology of the CSF. Teratoma almost always exhibit calcific, lipomatous or cystic foci. Clinical diagnosis based on MRI findings is a benign pineal cyst.

The pituitary cyst and sphenoidal cyst were clearly separated in the operation and in the MRI findings. The relationship between these forms of cystic degeneration and the pineal tumor is unknown. There are, however, no papers concerning these complicating and autoimmune disorders. It appeared that there was no relation between antipituitary antibodies and these three disorders.

Acknowledgement

The secretarial help of Mrs. Akiko Kawakami is greatly appreciated.
References


