Hypothalamic Type of Hypopituitarism and Central Diabetes Insipidus Probably Linked to Rathke’s Cleft Cyst

Tomoko Asano, Hodaka Yamada, Masashi Yoshida, Atsushi Aoki, Aki Ikoma, Ikuyo Kusaka, Hideo Toyoshima, Masafumi Kakei and San-e Ishikawa

Abstract

A 73-year-old woman was admitted due to weight loss and generalized malaise. The basal levels of all the anterior pituitary hormones, except for prolactin, were reduced. However, they were all elevated in response to exogenous hypothalamic hormones. After starting hydrocortisone replacement, the patient had polyuria of >5,000 mL/day. T1-weighted MRI depicted a low signal of an oval mass in the sella turcica and an iso-intense signal of another mass at the pituitary stalk. These findings indicate a hypothalamic type of hypopituitarism and masked central diabetes insipidus which possibly derived from the atypical occupation of Rathke’s cleft cyst at the pituitary stalk.

Key words: Rathke’s cleft cyst, hypothalamic type of hypopituitarism, central diabetes insipidus


Introduction

The widespread use of imaging modalities, such as computed tomography (CT) and magnetic resonance imaging (MRI), is increasing the incidental discovery of pituitary masses. In one study, pituitary microadenoma was discovered in 55% of patients undergoing brain imaging for investigation of symptoms not relevant to a pituitary mass (1). Patients with pituitary masses often have various symptoms related to excessive hormone production, the mechanical effect of an expanding tumor within the sella turcica and impaired pituitary function.

In this way, a space-occupying lesion, which does not produce hormones, may cause hypopituitarism by mechanisms including the diminished release or secretion of hypothalamic hormones, interruption of the delivery of hypothalamic hormones to the pituitary, and the loss or destruction of pituitary cells as a result of ischemia or necrosis (2). Furthermore, Arafah et al. suggested that increased intrasellar pressure has a predominant role in the pathogenesis of hypopituitarism in patients with pituitary adenoma (3). For symptoms and/or endocrinopathy caused by a space-occupying lesion, the precise location of the lesion must be determined.

In hypopituitarism, tumors occur in the hypothalamus (e.g., germinomas) or in the sella turcica (e.g., craniopharyngiomas) and compress the hypothalamus. During these conditions, the production and secretion of hypothalamic hormones and arginine vasopressin (AVP) are impaired, and the patients often have central diabetes insipidus and hypopituitarism. In an intrasellar lesion, such as a pituitary tumor or Rathke’s cleft cyst (RCC), patients typically have hypopituitarism and sometimes diabetes insipidus. In a pituitary stalk lesion caused by tumor, inflammation or congenital abnormalities (including RCC), patients have various endocrinopathy, namely hypopituitarism, central diabetes insipidus or both.

In the present study, we report a case of hypopituitarism and central diabetes insipidus which was probably associated with RCC. In particular, the patient’s endocrine dysfunction was found to come from a space-occupying lesion at the pituitary stalk level which was revealed to be the hypothalamic type of hypopituitarism.

Case Report

In July 2011, a 73-year-old woman presented with head-
achieve, generalized malaise, and poor appetite. When she went to a local hospital, the laboratory data showed her free thyroxine (T4) was 0.6 ng/dL, free triiodothyronine (T3) was 2.7 pg/mL, thyroid-stimulating hormone (TSH) was 0.6 μU/mL, and anti-thyroglobulin antibody was positive. She was diagnosed as having primary hypothyroidism and was treated with 25 μg/day of levothyroxine sodium for 2 weeks. After she took levothyroxine sodium, her generalized malaise became worse. Due to ophthalmologia, the patient visited an ophthalmologist, but she was not diagnosed with any particular disorder. She continuously complained of generalized malaise and poor appetite and visited another physician in August 2011. MRI was carried out and indicated a space-occupying lesion in the sella turcica. In August 2011, the patient was admitted to Jichi Medical University Saitama Medical Center for further evaluation.

The patient’s physical findings on admission were as follows: height, 147 cm; body weight, 47.7 kg; body mass index, 22.0; blood pressure, 114/81 mmHg without postural change; and pulse rate, 96 beats/min with a regular rhythm. No edema was noted in her legs or feet. She had no eyebrow, axillary or pubic hair loss. There were no abnormal findings on her head, neck, chest or abdomen. She had bilateral visual field defect. Laboratory findings were as follows: white blood cell count, 7,520/mm$^3$; neutrophils 57.9%, lymphocyte 28.3%, monocyte 6.3%, eosinophils 3.1% and basophils 2.1%; red blood cell count, 387×10$^6$/mm$^3$; hemoglobin, 12.6 g/dL; hematocrit, 35%; and platelets, 30.5×10$^4$/mm$^3$. The patient’s serum sodium (Na) level was 140 mmol/L; potassium, 4.1 mmol/L; chloride, 105 mmol/L; blood urea nitrogen, 8 mg/dL; serum creatinine, 0.8 mg/dL; uric acid, 4.3 mg/dL; serum C-reactive protein (CRP), 0.74 mg/dL; fasting plasma glucose, 90 mg/dL; hemoglobin A1c (NGSP), 6.2%; total cholesterol, 197 mg/dL; high density lipoprotein (HDL) cholesterol, 24 mg/dL; and triglyceride, 139 mg/dL.

In assessing the pituitary-adrenal axis, the patient’s plasma adrenocorticotropic hormone (ACTH) level was 9.5 pg/mL with serum cortisol levels of 1.1 μg/dL (Table). The corticotrophin-releasing hormone (CRH) challenge test showed a prompt increase in ACTH. The peak level of plasma ACTH was 76.6 pg/mL at 30 minutes (Fig. 1a). Regarding gonadotropin, both her serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels were markedly reduced. The luteinizing hormone-releasing hormone (LH-RH) challenge test showed a delayed increase in serum FSH, but the responses to exogenous LH-RH were minimal (Fig. 1b). The patient’s serum TSH was 0.23 μU/mL, and the serum free T4 and free T3 were 1.03 ng/dL and 2.88 pg/mL, respectively. Her serum prolactin (PRL) level peaked at 127.1 ng/mL. Her serum TSH level promptly, but insufficiently, increased in response to exogenous thyrotropin-releasing hormone (TRH) (Fig. 1c). Her serum growth hormone (GH) level was 0.186 ng/mL and insulin growth factor (IGF)-1 was 46 ng/mL. The growth hormone-releasing hormone (GH-RH) challenge test showed a prompt increase in GH release, but its response remained low (Fig. 1d).

The patient’s urine volume was 800 mL/day at examination. After being prescribed 15 mg/day hydrocortisone replacement, her urine volume dramatically increased to >5,000 mL/day and urinary osmolality was 112 mmol/kg. Four days later her Na and plasma osmolality elevated to 150 mmol/L and 306 mmol/kg, respectively. Her plasma AVP level was 0.6 pg/mL despite a plasma osmolality of 306 mmol/kg.

Space-occupying lesions were located at the pituitary stalk and pituitary gland and the optic chiasma was compressed by the lesion. T1-weighted MRI showed a low signal intensity of an oval mass in the sella turcica concomitantly with an iso-intense signal of another mass at the pituitary stalk (Fig. 2). The rim of the masses was enhanced by gadolinium. T2-weighted MRI showed that both masses became high signals at the pituitary stalk and pituitary gland. However, high signal intensity of the posterior pituitary disappeared.

We performed extensive examinations to determine the pathological states of the patient’s diabetes insipidus and hypopituitarism. As noted earlier, she had masked central diabetes insipidus and hypothalamic type of hypopituitarism.

### Table. Basal Plasma or Serum Levels of Various Hormones and Urinary Excretion of the Hormones and their Metabolites during the Patient’s Hospitalization

<table>
<thead>
<tr>
<th>(Hormones associated with CRH)</th>
<th>(Hormones associated with GH-RH)</th>
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<tbody>
<tr>
<td>ACTH 9.5 pg/mL (7.4-55.7)</td>
<td>GH 0.186 ng/mL (0.010-3.607)</td>
</tr>
<tr>
<td>Cortisol 1.1 μg/dL (4.0-18.4)</td>
<td>IGF-1 46 ng/mL (60-180)</td>
</tr>
<tr>
<td>Aldosterone 158 pg/mL (36-240)</td>
<td>AVP 0.6 pg/mL (0.3-3.5)</td>
</tr>
<tr>
<td>(Hormones associated with LH-RH)</td>
<td>(Hormones associated with AVP)</td>
</tr>
<tr>
<td>LH &lt;0.1 mU/mL (0.79-5.72)</td>
<td></td>
</tr>
<tr>
<td>FSH 1.43 mU/mL (2.0-8.3)</td>
<td></td>
</tr>
<tr>
<td>(Hormones associated with TRH)</td>
<td></td>
</tr>
<tr>
<td>TSH 0.232 μU/mL (0.35-4.94)</td>
<td></td>
</tr>
<tr>
<td>Free T4 1.03 ng/dL (0.70-1.48)</td>
<td></td>
</tr>
<tr>
<td>Free T3 2.88 pg/mL (1.71-3.71)</td>
<td></td>
</tr>
<tr>
<td>Anti-thyroglobulin Ab 86.6 IU/mL (&lt;40)</td>
<td></td>
</tr>
<tr>
<td>Prolactin 127.11 ng/mL (3.58-12.78)</td>
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**Note:** The table shows the basal plasma or serum levels of various hormones and urinary excretion of the hormones and their metabolites during the patient’s hospitalization.
including impaired secretion of CRH, LH-RH, and GH-RH, was strongly suggested. However, because she had takotsubo cardiomyopathy, an insulin-induced hypoglycemia test could not be performed. Radiological examinations strongly indicated that her endocrine disorders were derived from an intrasellar space-occupying lesion. However, we could not accurately diagnose whether the mass was a cystic neoplasm (such as a craniopharyngioma) or a cystic lesion (such as RCC). We initially suspected the mass was a craniopharyngioma and therefore suggested surgical therapy. However, the patient hesitated to undergo operation, and thus we observed her for a few months. She began replacement therapy with 1-desamino-8-D-arginine vasopressin (DDAVP) (10 μg/day), hydrocortisone (15 mg/day), and levothyroxine (25 μg/day). After initiating intranasal administration of DDAVP, the patient had sufficient urinary concentration. Her main symptoms of generalized malaise, appetite loss and headache disappeared.

Eight days after hydrocortisone and DDAVP replacement, the patient lost consciousness for a few minutes while sitting on the toilet. An electrocardiogram (ECG) showed inverted T waves in all V1-6 (Fig. 3), and an echocardiogram revealed left ventricular dysfunction with apical dyskinesis. The laboratory findings did not show any change in serum creatine kinase (CK), CK-MB or troponin T levels. A week later, the echocardiogram showed normal contraction and ejection fraction. We diagnosed the patient with takotsubo cardiomyopathy. After a year, the patient’s ECG indicated normal T waves.

Three months later, the patient’s MRI was reexamined. T1-weighted MRI depicted that the previously iso-intense mass at the pituitary stalk was markedly reduced and appeared as a high signal intensity (Fig. 2e, f). Inversely, the mass appeared as a low-intense mass on the T2-weighted MRI. Also, the swelling of the pituitary stalk and pituitary gland disappeared. These morphological findings may suggest RCC. However, although the mass at the pituitary stalk was reduced on MRI, the patient’s panhypopituitarism and central diabetes insipidus remained unchanged.

Discussion

MRI showed two cystic lesions located at the pituitary stalk and intrasellar space in the present patient, and they spontaneously reduced in size 3 months later. The intensity on T1-weighted MRI became low to high during the 3-month observation period. These morphological findings may suggest the probability of RCC. If the mass is RCC, it did not cause endocrinopathy for long. When the size of a mass becomes enlarged by hemorrhage or inflammatory changes (such as in the present case), the pituitary stalk may be compressed by the mass. Another possibility is that inflammation related to the mass may also involve the pituitary stalk. Such changes produce atypical endocrinological disorder, thus disrupting the descending flow of hypothalamic hormones, and resulting in a hypothalamic type of hypopituitarism and central diabetes insipidus. However, the patient’s hypopituitarism remained unchanged after the reduction of the mass at the pituitary stalk.

The most notable finding was that the patient’s hormonal deficiency was closely related to hypothalamic types of disorder. She had central diabetes insipidus and impaired secretion of hypothalamic hormones. The basal levels of all the patient’s anterior pituitary hormones, except for prolactin, decreased; however, they were elevated after the stimulation of exogenous hypothalamic hormones. The patient’s ACTH, GH and TSH levels responded well to exogenous administration of CRH, GH-RH and TRH, respectively. A weak

Figure 1. The endocrinological data of the various challenge tests for pituitary hormones. (a) CRH challenge test, (b) LH-RH challenge test, (c) TRH challenge test, (d) GH-RH challenge test.
response of gonadotropin to exogenous LH-RH was also obtained. Because she had takotsubo cardiomyopathy after admission, we could not perform an insulin-induced hypoglycemia test. The patient’s serum prolactin level was also elevated. Therefore, the endocrinological disorder indicated here may be based on the hypothalamic type of hypopituitarism.

MRI showed cystic lesions in suprasellar and intrasellar spaces without any abnormality in the hypothalamus. These cystic lesions had no calcification and their rims were irregularly thick and the shape of sella turcica remained unchanged. Furthermore, the lesions spontaneously decreased.

Figure 2. Brain magnetic resonance imaging (T1-weighted MRI). (a) Plain MRI, sagittal view at the admission, (b) Plain MRI, coronal view at the admission, (c) Enhanced MRI, sagittal view at the admission, (d) Enhanced MRI, coronal view at the admission, (e) Plain MRI, sagittal view three months after the admission, (f) Plain MRI, coronal view three months after the admission.
In the present case, the inflammatory expansion to the pituitary stalk may have caused hypothalamic type of hypopituitarism and diabetes insipidus. Our patient’s endocrinological abnormality persisted even after the improvement of the cystic lesion on MRI. Surgical removal of the content of RCC may not improve the endocrinological dysfunction.

The patient had takotsubo cardiomyopathy after admission. Takotsubo cardiomyopathy is a stress-induced cardiomyopathy which is frequently, but not always, triggered by an acute medical illness or by intense emotional or physical stress. Postulated mechanisms include catecholamine excess, multiple vessel coronary artery spasm and microvascular dysfunction. Takotsubo cardiomyopathy is also known to be caused by pheochromocytoma. However, takotsubo cardiomyopathy is very rare in patients with hypopituitarism.

In the literature, few takotsubo cardiomyopathy cases have so far presented with adrenal failure (24-28). Our patient suffered from takotsubo cardiomyopathy seven days after the hydrocortisone replacement therapy. Thus, adrenal failure may be ruled out as the likely cause of takotsubo cardiomyopathy. Because she had had physical and mental stress for a few months, we believe that the takotsubo cardiomyopathy may be indirectly related to secondary adrenal failure due to hypothalamic hypopituitarism.

The authors state that they have no Conflict of Interest (COI).

**References**


7. Hamilton BE, Salzman KL, Osborn AG. Anatomic and pathologic change of RCC may have disappeared spontaneously, but the possibility that the physiological dose of hydrocortisone may have improved the inflammation of RCC in our patient could not be ruled out (23). Enlargement of RCC due to inflammatory change may block the pituitary portal circulation and induce axonal degeneration of the hypothalamo-neurohypophysial system at the pituitary stalk. Such abnormalities caused endocrinological “hypothalamic dysfunction,” resulting in hypopituitarism and central diabetes insipidus. Our patient’s endocrinological abnormality

8. Figure 3. Time course of electrocardiogram. (a) on admission, (b) 8 days after the admission