A Case of Schmidt Syndrome Accompanied by a Pituitary Adenoma

FUMIO OTSUKA, TOSHI OGURA*, NOBUHIKO HAYAKAWA, MASAMI HASHIMOTO, HIROFUMI MAKINO, ZENSUKE OTA, AND JINGO KAGEYAMA**

Third Department of Internal Medicine, Okayama University Medical School, and *Health and Medical Center, and **Department of Nursing, School of Health Sciences, Okayama University, Okayama 700, Japan

Abstract. Schmidt syndrome consists of adrenal insufficiency and Hashimoto's thyroiditis, which are probably caused by an autoimmune process. We encountered a patient who manifested severe generalized fatigue due to Schmidt syndrome recurrently. The endocrinological examination tests on the patient showed that the increase in thyroid stimulating hormone (TSH) and ACTH concentrations were not remarkable, despite hypo-function of the peripheral glands. Subsequent cranial magnetic resonance imaging (MRI) exhibited the existence of a pituitary tumor. The pathological findings on the resected tumor and endocrinological stimulation tests proved that the tumor was a FSH-producing adenoma. Although involvement of the pituitary region in Schmidt syndrome on rare occasions presents as hypophysitis, no pituitary adenoma has previously been reported in association with this syndrome. We present a patient with Schmidt syndrome and an accompanying FSH-producing pituitary adenoma. The coexistence of these disorders suggests that the functioning pituitary tumor might be considered as a pituitary lesion in Schmidt syndrome.

Key words: Schmidt syndrome, Autoimmune polyglandular syndrome (APS), Addison's disease, Hashimoto's disease, Gonadotropinoma, FSH-producing pituitary adenoma

SINCE Schmidt described the clinical course and autopsy findings in two patients with adrenal insufficiency due to destructive lymphocytic infiltration of both the thyroid and adrenal cortex in 1926 [1], a large number of studies and case reports of this disorder have accumulated. An autoimmune mechanism associated with Schmidt syndrome has been suggested.

Since Neufeld advocated the concept of polyglandular autoimmune (PGA) syndrome and classified it into the major two types in 1981 [2], this syndrome has also been termed "polyglandular failure syndrome", "organ-specific autoimmune disease", "polyendocrinopathy diabetes", and "autoimmune polyglandular syndrome (APS)". Schmidt syndrome has been included in the definition of APS type 2. Although the pituitary lesions in APS on rare occasions present as hypophysitis [3], no reports on APS associated with a pituitary adenoma have been published. We encountered a patient with Schmidt syndrome accompanied by a gonadotroph adenoma.

Case Report

A 55-year-old Japanese man suffered recurrent episodes of severe generalized fatigue and muscle weakness during the summer. Although he was repeatedly hospitalized, the cause of these attacks
remained unclear and he was frequently treated with saline infusions. In the past three years his body weight decreased by approximately 10 kg and hair loss appeared. He was hospitalized as an emergency case in March 20, 1995, because of fever, severe fatigue, muscle weakness, visual disturbances, vomiting and diarrhea since the early part of March, 1995. On admission, his level of consciousness was decreased and he appeared drowsy. Hypotension (blood pressure: 70/50 mm Hg), hypothermia (body temperature: 35.3 °C), hyponatremia (Na: 111 mEq/l) and metabolic acidosis (base excess: -7 mEq/l) were all found. On endocrinological examination, the following serum and plasma concentrations were determined: free triiodothyronine, 1.8 pg/ml; free thyroxine, 0.7 ng/dl; thyroid stimulating hormone (TSH), 7.05 µU/ml; cortisol, <1.0 µg/dl; and ACTH, 48 pg/ml. After levothyroxine sodium (50 µg/day) and hydrocortisone (25 mg/day) were administered as replacement therapy for hypothyroidism and adrenal insufficiency, he was transferred to our hospital. On physical examination in our hospital, he was alert, with a temperature of 36.2 °C, a heart rate of 70 beats/min, and blood pressure of 99/70 mm Hg. His skin was dry, but without abnormal pigmentation, and he had no struma or lymphadenopathy. Auscultation of the lungs and heart revealed no abnormality. Surgical scars due to partial lobectomy for a hepatic hemangioma were present on his abdominal wall. The examination of visual fields revealed bitemporal hemianopsia. The size, shape and location of testis were normal. Laboratory data included a red blood cell count of 3.52 x 10⁶/µl, and a hemoglobin concentration of 11.4 g/dl; Serum concentrations of total protein, electrolytes, and immunoglobulin were normal, as were the results of liver and renal function tests. The results of blood gas analysis also were normal. Values obtained from endocrinological examination on admission in our hospital are shown in Table 1. Despite replacement therapy with cortisol and thyroxine, the ACTH (48.4 pg/ml) and TSH (6.08 µU/ml) concentrations were increased. PRL and FSH concentrations of 53.7 ng/ml, and 56.12 µU/ml, respectively, also were increased, and the plasma aldosterone (PAC) and dehydroepiandrosterone sulfate (DHEA-S) concentrations were decreased at 40.3 pg/ml, and 15 µg/dl, respectively. The serum testosterone concentration was 4.4 ng/ml, within normal limits. Of the autoimmune antibodies, the anti-thyroglobulin (TG) antibody was detected (>100 U/ml), but the anti-thyroid peroxidase (TPO) antibody was not. Both microsome hemagglutination (MCHA) and thyroglobulin hemagglutination (TGHA) tests were highly positive. In addition, anti-parietal cell and anti-nuclear antibodies also were detected (Table 2). Although on endocrinological stimulation tests of adrenal gland hormones, serum cortisol showed almost no response to the administration of 250 µg of ACTH compared to increases in PAC (Fig. 1A), serum and urine free cortisol concentrations increased to the normal range in response to a 3-day-continuous administration of 1 mg of ACTH-Z (Fig. 1B). The overnight dexamethasone
SCHMIDT SYNDROME AND PITUITARY ADENOMA

Table 2. Immunological examination data on admission

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Value</th>
<th>Antibody</th>
<th>Value</th>
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<tbody>
<tr>
<td>Anti-TPO antibody</td>
<td>&lt;0.3 U/ml</td>
<td>Anti-adrenal cortex antibody</td>
<td>(−)</td>
</tr>
<tr>
<td>Anti-TG antibody</td>
<td>&gt;100 U/ml</td>
<td>Anti-pituitary antibody</td>
<td>(−)</td>
</tr>
<tr>
<td>MCHA</td>
<td>× 400</td>
<td>Anti-parietal cell antibody</td>
<td>× 20</td>
</tr>
<tr>
<td>TGHA</td>
<td>× 6400</td>
<td>Anti-intrinsic factor antibody</td>
<td>(−)</td>
</tr>
<tr>
<td>TBII</td>
<td>0 % (&lt;15)</td>
<td>Anti-islet cell antibody</td>
<td>(−)</td>
</tr>
<tr>
<td>TSBAb</td>
<td>&lt;1 % (&lt;40)</td>
<td>Anti-mitochondria antibody</td>
<td>(−)</td>
</tr>
<tr>
<td>Anti-nuclear antibody × 80, homogeneous</td>
<td></td>
<td>Anti-smooth muscle cell antibody</td>
<td>(−)</td>
</tr>
<tr>
<td>Anti-DNA antibody</td>
<td>(−)</td>
<td>Anti-myocardial antibody</td>
<td>(−)</td>
</tr>
<tr>
<td>Anti-AChR antibody</td>
<td>(−)</td>
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TPO, thyroid peroxidase; TG, thyroglobulin; MCHA, microsome hemagglutination; TGHA, thyroglobulin hemagglutination; TBII, TSH-binding inhibitory immunoglobulin; TSBAb, thyroid stimulation blocking antibody; AChR, acetylcholine receptor.

Fig. 1. Endocrinological stimulation tests of adrenal hormones. The serum cortisol concentration showed almost no response to the intravenous administration of 250 µg of adrenocorticotropin (ACTH) in contrast to the increase in the plasma aldosterone concentration (A). Serum and urine free cortisol concentrations increased to the normal range in response to the 3-day-continuous administration of 1 mg of ACTH-Z (B).

Fig. 2. 131I-labelled adosterol scintigraphy. 131I-labelled adosterol scintigraphy exhibited no accumulation of tracer in either adrenal gland.

(1 mg) suppression test caused an immediate lowering of the high ACTH concentration. Although computed tomography (CT) showed the adrenal gland to be of normal shape and size, 131I-labelled adosterol scintigraphy exhibited no accumulation of tracer in either adrenal gland (Fig. 2). Although endocrinological stimulation tests of anterior pituitary hormones, including corticotropin-releasing hormone (CRH), GH-releasing hormone (GRH), and thyrotropin-releasing hormone (TRH), showed normal responses, LHRH stimulation test demonstrated hyper-responsiveness of FSH compared with LH (Fig. 3). An oral glucose (75 g) tolerance test demonstrated a decrease in the blood glucose
concentration for 3 h, and transient increase in the serum immunoreactive insulin concentration. GH gradually decreased in response to the high blood glucose level. Cranial magnetic resonance imaging (MRI) exhibited a pituitary tumor involving the undersurface of the sella turcica with compression of the optic chiasma. The tumor appeared as a region of high intensity signal on T1-WI and was well-enhanced by Gd-DTPA (Fig. 4).

The patient was diagnosed with Schmidt syndrome accompanied by a pituitary adenoma, and underwent transsphenoidal surgery for the pituitary tumor on March 25, 1995. The resected pituitary tumor was pathologically compatible with a pituitary adenoma (Fig. 5A), and immunological staining for the β-FSH monoclonal antibody proved the tumor to be an FSH-producing pituitary adenoma (Fig. 5B). Postoperatively, the patient underwent repeat endocrinological stimulation tests of the anterior pituitary hormones. With the administration of LHRH, the FSH response normalized, and the GH and PRL responses were slightly augmented (Fig. 6). The administration of hydrocortisone (30 mg/day) and levothyroxine sodium (50 μg/day) was continued, and the patient achieved a well-controlled state.

**Discussion**

Schmidt syndrome is a disorder which is a complication of idiopathic Addison's disease and Hashimoto's disease [1]. This disorder has recently been recognized to involve not only the endocrine organs, but also the skin, gastrointestinal system, liver, bone marrow and heart [2]. This
disorder is rare in Japan, and its pathogenesis and relationship with human leukocyte antigen (HLA) has not been clarified [4].

This case was diagnosed on the basis of adrenal insufficiency and hypothyroidism, because of the patient's recurrent generalized fatigue. On the initial disease manifestation, the increases in TSH and ACTH concentrations were unremarkable, despite the presence of primary hypothyroidism and adrenal insufficiency. This suggests the existence of a pituitary adenoma which caused a visual field disturbance and suppressed pituitary secretion, and therefore the initial endocrinological examination data were complicatedly modified. Although the basal hormone values for the adrenal cortex, including cortisol, aldosterone, and DHEA-S, were decreased, the adrenal medulla had not been damaged. On the rapid ACTH stimulation test, aldosterone, but not cortisol, yielded a response. Because serum and urine cortisol concentrations were slightly increased in the continuous ACTH-Z stimulation test, it was suggested that the function of the zona fasciculata of the adrenal cortex partially remained. This partial reserve of the adrenal function was compatible with idiopathic Addison's disease. And because the increased ACTH concentration was easily suppressed by 1 mg of dexamethasone, the ACTH had evidently not been autonomously secreted. Although the adrenal gland appeared morphologically normal on CT, damage to the adrenal cortical function was proven by defects in accumulation on 131I-labelled aldosterol scintigraphy. On the other hand, although the patient's hypothyroidism was thought to have been induced by an autoimmune mechanism (based on the existence of anti-TG antibodies, TGHA and MCHA), aspiration biopsy findings for the thyroid gland revealed no cell infiltration. Other immunological examinations revealed the presence of anti-nuclear and anti-parietal cell antibodies. This complicated endocrinopathy was therefore diagnosed as Schmidt syndrome, namely, autoimmune polyglandular syndrome (APS), type 2 as defined by Neufeld in 1981 [2]. APS type 2 has been reported to accompany idiopathic Addison's disease, autoimmune thyroiditis, insulin-dependent diabetes mellitus (IDDM), pernicious anemia, hypogonadism, alopecia and vitiligo [2]. Although a low urinary C-peptide concentration suggests the existence of IDDM, IDDM may be masked by the cortisol deficiency and hypothyroidism. This patient should there-
fore be periodically reevaluated both endocrino-
logically and immunologically, because these
endocrinopathies may gradually become manifest
over the years [5, 6].

On the other hand, the gonadotropinoma affect-
ed the preoperative pituitary basal hormone con-
centrations, which did not show hyper-secretion
 corresponding with the hypofunction of the
peripheral endocrine glands. There have been oth-
er reports documenting pituitary hyperplasia and
adenomas in response to target endocrine gland
failure (especially in the thyroid) [7–11], as well as
hypopituitarism attributable to autoimmuno-hypo-
physitis in APS [3, 12, 13], but there have been no
descriptions of an FSH-producing tumor associat-
ed with Schmidt syndrome. Since serum
testosterone was normal and there were no clini-
cal findings of hypogonadism in this case, we
cannot possibly explain that this patient’s patho-
genesis is hyper-secretion of FSH followed

Fig. 5. Pathological findings in the removed pituitary tumor. The
pathological appearance of the resected tumor was consistent with
a pituitary adenoma on hematoxylin-eosin staining (× 100) (A). Immu-
nochemical staining for the β-FSH monoclonal antibody proved
the tumor to be an FSH producing adenoma (× 100) (B).
hypo-gonadism. There are also important findings indicating that the pituitary enlargement corresponding to the target peripheral endocrine gland failure can be diminished by replacement therapy with peripheral hormones [7–10]. Moreover, in APS, the accompanying hypophysitis presents as swelling of the pituitary gland with lymphocytic infiltration [14]. Although these findings suggest that in this case gonadotroph adenoma coincided with APS incidentally, we cannot neglect the possibility that APS affected the development of the pituitary adenoma. Although functioning tumors which produce TSH, GH or PRL may be associated with PIT-1 transcription factor [15], we could not identify any growth stimulating factors for FSH-production. This case suggested that the pituitary adenoma should be taken into consideration as a pituitary lesion in Schmidt syndrome, and indicated the possibility that some growth factor developing the functioning pituitary tumor which did not correspond to the peripheral gland failure would exist. To further investigate these factors, we hope to accumulate more case reports of this endocrinologically rare condition to assist in our understanding of the coincidence of APS and pituitary tumors.

References


