Spontaneous Recovery from Pathologically Confirmed Lymphocytic Adenohypophysitis with a Dramatic Reduction of Hypophyseal Size

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A pituitary mass compressing the optic nerve was revealed by magnetic resonance imaging (MRI) in a 35-year-old woman complaining of visual disturbance in the post-partum period. Responses of plasma gonadotropin and corticotropin-cortisol levels to respective hypothalamic hormones were delayed or blunted, but the response of plasma prolactin to thyrotropic-releasing hormone was exaggerated. Diabetes insipidus was not associated. Biopsy revealed lymphocytic adenohypophysitis, and no hypophysectomy was performed. Only five weeks later, the pituitary mass spontaneously disappeared on MRI. The pituitary function was normalized. Anti-thyroidal and anti-pituitary antibodies were negative throughout the clinical course. Pituitary masses developing during late pregnancy or the post-partum period should be carefully observed.

Key words: hypopituitarism, autoimmune hypophysitis, hyperprolactinemia

Introduction

Lymphocytic adenohypophysitis (LAH) has been increasingly recognized as a cause of hypopituitarism especially in women during late pregnancy or during the postpartum period (1–3). Since the first report in 1962 (4), more than 100 cases have been reported. Usually this disease is characterized by a growing pituitary tumorous lesion with partial or pan-hypopituitarism. Pathologically, lymphocytes and plasma cells diffusely infiltrate the pituitary gland, and the pituitary cells are damaged (3–7). An autoimmune mechanism may underlie the pathogenesis of this disorder. However, the natural course of this disease is not known in detail. It has been considered that this disease results in variable degrees of permanent hypopituitarism including lethal adrenal insufficiency. On the other hand, several suspected patients with spontaneous recovery were reported (8–16). Among them, however, few reports have included endocrine, imaging and pathological studies. We observed a woman with LAH who recovered spontaneously without any medication or other intervention except for hypophyseal biopsy and report this case with several examinations in detail.

Case Report

A 35-year-old woman noticed visual disturbance in the 36th week of pregnancy in May, 1998 (Fig. 1). She had previously experienced pregnancy twice at the age of 28 and 32 years old. However, she had artificial and spontaneous abortion, respectively. She consulted the neurology department of a hospital. However, no detailed examination was performed because of the pregnancy. Two weeks after the delivery in the 38th week of pregnancy by cesarean section on June 9, the visual disturbance advanced, and visual field examination showed bitemporal quadrantanopsia. Brain computed tomography revealed a large pituitary mass lesion. She was referred to the Department of Neurosurgery of Gifu City Hospital for the purpose of pituitary surgery. No fatigue, thirst, polyuria, polydipsia, headache, vertigo or dizziness was seen on admission. Breast-feeding was not performed and menstruation was seen at the end of August. However, the visual disturbance was sustained. Physical examination was unremarkable. Magnetic resonance imaging (MRI) revealed a pituitary mass lesion showing suprasellar extension and compression of the optic nerve and homogeneously enhanced with gadolinium on July 9, 1998 (Fig. 2A).

A simultaneous intravenous administration of 100 μg gona-
Yamakita et al

36th week Delivery of pregnancy (Jun. 9) Pituitary biopsy (Aug. 13)

Subjective visual disturbance

Visual field

bitemporal II bitemporal I normal normal

visual field

quadranantanopia (July 10) (Oct. 15)

Large pituitary mass on CT

Large pituitary mass on MRI (Fig. 2A, July 9)

Brain CT or MRI

Dramatic reduction of pituitary mass on MRI (Fig. 2B, Oct. 14)

No pituitary enlargement on MRI (Jan. 26)

Endocrine examination

1st loading tests for pituitary hormones (Fig. 3, Aug. 11)

2nd loading tests for pituitary hormones (Fig. 3, Oct. 15)

3rd loading tests for pituitary hormones (Fig. 3, Jan. 26)

May Jun July Aug Sep Oct Nov Dec Jan Feb '98 '99

dotropin-releasing hormone (GnRH), 100 µg growth hormone-releasing hormone (GHRH), 100 µg corticotropin-releasing hormone (CRH), and 500 µg thyrotropin-releasing hormone (TRH) on Aug 11 showed slightly blunted or delayed increase of plasma levels of luteinizing hormone (LH), from less than 0.5 IU/l to 5.2 IU/l, follicle-stimulating hormone (FSH), from 2.6 to 13 IU/l, corticotropin (ACTH), from 2.86 to 3.96 pmol/l, and cortisol, from 138 to 276 nmol/l (Fig. 3). However, the basal plasma prolactin level was high, 20 µg/l, and it markedly increased to 86 µg/l. The responses of plasma growth hormone (GH) and thyrotropin (TSH) were normal. Anti-pituitary antibody reaction with the cytosol of rat pituitary cells using a biotin/avidin detecting technique (17) was negative. Serum levels of free triiodothyronine (fT3) and free thyroxin (fT4) were within the normal ranges, 3.12 pmol/l and 13.1 pmol/l, respectively. Anti-thyroidal peroxidase antibody and anti-thyroglobulin antibody were negative. The serum estradiol level was low, 29.4 pmol/l. The urinary volume was 980–1,450 ml/day and the specific gravity of the urine was 1.019–1.021, although the posterior lobe function was not examined in detail. Just before the operation she felt a slight amelioration of the visual acuity, but no change was seen in the visual field examination. Biopsy of the pituitary was performed two days after the pituitary-loading test (Fig. 1), and glucocorticoid was not administered before the operation. During the transsphenoidal pituitary surgery, no tumor tissue was found macroscopically and only a biopsy was performed. After the operation, the visual disturbance gradually improved and the patient was discharged.

On Oct 14, 1998, she was referred to the Endocrine Division of Matsunami General Hospital for further evaluation of her pituitary function. The mass lesion of the pituitary disappeared and the pituitary size became normal on MRI (Fig. 2B). Plasma LH and FSH responses to 100 µg GnRH were normalized, from 3.5 IU/l to 33 and from 7.7 IU/l to 30, respectively. The responses of plasma ACTH and cortisol to the intravenous administration of 100 µg CRH were also normal, from 4.6 pmol/l to 13.7 and from 395 nmol/l to 624, respectively. The responses of plasma GH and TSH to 100 µg GHRH and 100 µg TRH were similarly normal, respectively. However, the basal plasma prolactin level was still high, 24 µg/l, and it was markedly increased to 74 with stimulation with 100 µg TRH (Fig. 3). Serum fT3 and fT4 were normal, 2.98 pmol/l and 10.9 pmol/l. The plasma estradiol level became normal, 111.2 pmol/l. Plasma and urine osmolarity and plasma antidiuretic hormone level normally changed from 292 mmol/kg, 196 mmol/kg and 1.4 ng/l to 294, 628 and 1.8 after the overnight-water restriction, respectively. Anti-pituitary cytosol antibody described before was negative at this time, too.

On Jan. 26, 1999, the general condition of the patient was very good, and physical examination was unremarkable. The

Figure 1. Clinical course of the patient. Arrow indicates the date of each item.
Remission from Lymphocytic Hypophysitis

Figure 2. Magnetic resonance imaging of the pituitary gland. A large pituitary mass lesion with suprasellar extension was revealed. It was homogeneously enhanced with gadolinium (July 9, 1998). A); The pituitary size was dramatically reduced. The shape and size of the pituitary gland were unremarkable (October 14, 1998). B); arrows, pituitary gland.

Pathological findings of the pituitary mass lesion

Small clusters of epithelial cells were identified in the edematous and fibrous tissue. Epithelial cells were atrophic. Lymphocytes and plasma cells infiltrated. Capillaries were dilated (Fig. 4).

Discussion

The MRI, endocrine, and pathological findings of the present patient were consistent with LAH. This disease is characterized by a pituitary mass lesion which usually causes hypopituitarism. However, diabetes insipidus is an unusual manifestation of this disease (12, 14, 16, 18). Lymphocytic infundibuloneurohypophysitis which was initially reported by Saito et al in 1970 (19) and was proposed as a clinical entity by Imura et al in 1993 (20) causing central diabetes insipidus is likely distinct from LAH and is not a variety of this disease. In the cases of the complication of diabetes insipidus with LAH, the inflammation occurring in the adenohypophysis might affect the function of the neurohypophysis. LAH frequently occurs in late pregnancy and the postpartum period (1–3). Pregnancy seems to play a particularly important role in the presentation of LAH.

An autoimmune mechanism may play a role in the pathophysiology of this disorder; that is, histological features of pituitary lesions (4–7), onset in late pregnancy or in the postpartum period (1, 5–7, 15), association with lymphocytic thyroiditis (1, 4, 13, 16, 21, 22), positive finding of anti-pituitary antibodies (1, 13, 23, 24), and the efficacy of glucocorticoid treatment (2, 25) all support an autoimmune role. Although no serological data showing an autoimmune anomaly were positive in the present patient as is similar to other reports (5, 9, 16, 18, 22), the pathological findings were compatible with LAH. We ex-
Figure 3. The responses of the plasma pituitary hormone levels to the intravenous administration of the respective hypothalamic hormones. The response of plasma luteinizing hormone (LH) level to gonadotropin-releasing hormone (GnRH) administration A); The response of plasma follicle-stimulating hormone (FSH) level to GnRH administration B); The response of plasma growth hormone (GH) level to GH-releasing hormone administration C); The responses of plasma corticotropin (ACTH) D) and cortisol E) levels to corticotropin-releasing hormone administration; The responses of serum thyrotropin (TSH) F) and plasma prolactin (PRL) G) levels to thyrotropin-releasing hormone administration. open circle: September, 1998, closed circle: October, 1998, open triangle: January, 1999.

Figure 4. Pathological findings of the pituitary gland. HE stain. x50. Infiltration of lymphocytes and plasma cells were found in the edematous and fibrous tissues. Epithelial cells were atrophic.

amined only the anti-pituitary antibody reacting with the cytosol of rat pituitary cells. While anti-rat pituitary antibodies, especially anticytosol antibodies, might sometimes be good indicators of the activity of autoimmune hypophysitis (13), the method of detecting pituitary antibodies and their pathogenic significance are still controversial subjects. Engelberth and Jezkova (26) noted high titers of anti-pituitary antibodies in sera of 18% of randomly sampled females in the immediate post-partum period. Kajita et al (27) reported that anti-pituitary antibodies were positive in 10 of 11 patients with several degrees of hypopituitarism.

It was reported in a review (1) that the hormone deficiency pattern in LAH is different from that in cases of pituitary adenoma. LAH frequently results in isolated ACTH deficiency or combined adrenal/thyroid deficiency in contrast with pituitary adenoma in which ACTH deficiency rarely occurs. Prolactin is the most variable hormone in LAH (1). Isolated hypogonadism occurred in association with hyperprolactinemia in a few patients (24, 28, 29), similar to the present patient. A stalk compression could be a cause of hyperprolactinemia (30). However, even after a great reduction of the pituitary size, hyperprolactinemia and the hyperresponse of prolactin were
seen in the present patient. Further, three months later, they became normal. It is more likely, accordingly, that the residual lactotroph hyperplasia from the recent pregnancy (31, 32) was the cause of this phenomenon.

Until recently, LAH had been a rare disease, and no diagnosis was made until hypophysectomy was performed. The natural history of LAH is not fully understood. In some cases, especially early cases, progressive severe and permanent hypopituitarism resulted in fatal complications. They were identified at autopsy. In 1980, the first living case was reported (28). Total hypophysectomy as a treatment induces an improvement of the symptoms, visual disturbance, headache, and/or dizziness owing to the large mass in the pituitary gland, but induces panhypopituitarism leading to the requirement for replacement therapy. Recently, MRI has become very popular, and the clinical entity of LAH has been more widely recognized. However, only a few patients with spontaneous recovery from LAH with histological confirmation have been reported other than the present patient (12, 15). When the suspected patients who were not diagnosed pathologically are included, several patients were reported to have shown spontaneous resolution (8-16, 33). However, the possibility that other types of hypophysitis, especially sarcoidosis or histiocytosis X was included among them was not completely excluded. The present patient underwent only pituitary biopsy and showed dramatic reduction of the pituitary mass only five weeks later and recovery from partial hypopituitarism. The pituitary lesion in this patient might not have been severe. It is likely that many pituicytes were conserved in spite of the infiltration of lymphocytes and plasma cells and the proliferation of fibroblasts. Edematous change rather than the destruction of pituicytes was severe from the result of the large mass on MRI. If a great number of pituicytes had been damaged by the inflammation, the patient would have fallen into permanent or partial hypopituitarism; this may be one of the causes of Sheehan’s syndrome (6). Regarding this point, it is unknown whether the inflammation in the pituitary is blocked by the treatment with glucocorticoids or other agents. Post-partum silent thyroiditis which is an autoimmune disease similar to LAH has been shown to be ameliorated more rapidly when treated with prednisolone compared to the non-treated control (34). It is reported that glucocorticoid treatment ameliorates the symptoms due to pituitary mass and hypopituitarism (25). However, usually glucocorticoid does not resolve the pituitary function completely (7). Even if the disease is self-limiting, it is unknown for how long and to what degree the pituitary inflammation continues and extends. In the present patient, progressive visual disturbance fortunately spontaneously improved probably due to mild inflammatory change of the pituitary. However, if the inflammation is more severe and visual disturbance is more rapidly progressive, it is unknown which is the better treatment, surgical exploration or administration of large doses of glucocorticoids.

When a pituitary mass lesion is discovered during late pregnancy or the post-partum period and LAH is suspected, immediate hypophysectomy is not always recommended. Instead, substitution therapy and follow-up should be selected. The clinical course, especially any progression of the visual disturbance and adrenal insufficiency should be carefully observed.

References