

NOTE

## Long-Term Clinical Course of Two Cases of Lymphocytic Adenohypophysitis

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**Abstract.** In two patients with lymphocytic adenohypophysitis, images of the pituitary gland were serially observed by MRI. In both cases, the pituitary gland had swollen during the late stage of the first pregnancy. In case 1, MRI findings were representative of lymphocytic adenohypophysitis. After delivery, plasma levels of PRL, ACTH and cortisol decreased markedly. The height of the pituitary gland gradually decreased from 22 mm (14 days after delivery) to 13 mm (73 days) and became rapidly smaller (4.9 mm, 115 days) following administration of massive doses of hydrocortisone for the treatment of acute adrenal insufficiency induced by painless thyroiditis. Six years later, the height was 2.5 mm. Low plasma levels of PRL and cortisol persisted. Diabetes insipidus did not develop. In case 2, MRI revealed a pituitary mass accompanied by a cystic change. Lymphocytic adenohypophysitis was confirmed by histological examination. Because pituitary function tests indicated that ACTH, PRL, GH and TSH were of low levels, hydrocortisone and L-thyroxine were orally administered. No diabetes insipidus was demonstrated. MRI disclosed that the height of the pituitary gland was 23 mm (17 days after delivery) but decreased to 17 and 5.5 mm after 44 and 128 days, respectively. Four years later immediately after the second delivery, it was 1 mm, and the patient was diagnosed as having empty sella. Long-term observation of lymphocytic adenohypophysitis demonstrated that the pituitary gland was markedly atrophied, leading to empty sella. It is believed that some of the classic cases of Sheehan's syndrome associated with empty sella may include lymphocytic adenohypophysitis.

*Key words:* Lymphocytic adenohypophysitis, Magnetic resonance imaging (MRI), Hypopituitarism, Empty sella, Sheehan's syndrome

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LYMPHOCYTIC adenohypophysitis [1] has been reported in a larger number of cases in Japan [2] than in the U.S. and European countries [3, 4], and is considered to be an autoimmune disease. Lymphocytic adenohypophysitis most frequently develops in women, especially in young females, and 70–90% of the cases occur during late pregnancy or in the postpartum period [3, 4]. Most of

the cases progress to either partial hypopituitarism or panhypopituitarism. We previously reported in an abstract [2] that during the follow-up of a patient with lymphocytic adenohypophysitis (case 1), magnetic resonance imaging (MRI) demonstrated that the swollen pituitary gland was gradually reduced in size postpartum and that it further rapidly shrank to its normal size following massive doses of hydrocortisone administered three months later. In the present study, we report changes in MRI studies and the clinical course of pituitary function over long periods of time in two cases including case 1.

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## Case Report

### Case 1

The patient was a 33-year-old woman who had experienced a visual field defect (bitemporal hemianopsia confirmed later) at 36 weeks of pregnancy at the age of 27. She delivered a baby by cesarean section at 39 weeks, and on August 25, 1989, and was admitted to our hospital for further evaluation. Goiter was impalpable, and postpartum lactation was not observed. Routine examination revealed no abnormal findings. On September 8, 1989, MRI disclosed a tumor image extending from the sella turcica to the suprasellar cistern with a lower signal intensity than that of the white matter on T<sub>1</sub> weighted images (Fig. 1) and a high signal intensity on T<sub>2</sub> weighted images. Gd-DTPA contrast images showed a symmetrical and homogeneous tumor pattern, but the posterior lobe of the pituitary gland appeared normal. The LH was <0.3 IU/l. The FSH (7.8 IU/l), PRL (12 μg/l), GH (1.6 μg/l) and cortisol (103 μg/l) levels were normal. T<sub>4</sub> was 53 μg/l, T<sub>3</sub> 0.7 μg/l and fT<sub>4</sub> 5.3 ng/l, which indicated mild hypothyroidism, but the TSH level was normal (Table 1). LHRH test revealed no response of LH and a delayed response of FSH. TRH test showed a normal response of TSH and no response of PRL. Insulin tolerance test showed a delayed response of GH and a normal response of cortisol (Fig. 2). Anti-GH<sub>3</sub> cell antibody and anti-thyroglobulin antibody were positive, but the anti-AtT<sub>20</sub> cell antibody was negative. Bitemporal hemianopsia improved, and slight reduction in the mass was confirmed by MRI after delivery on October 21, 1989. Her clinical course remained uneventful without treatment.

The clinical course and changes in endocrinological data are shown in Table 1. After one month, LH became detectable (5.6 IU/l), but PRL and cortisol decreased to 2.5 μg/l and 60 μg/l, respectively. After three months (December, 1989), since anorexia and fever suddenly developed and persisted, the patient was admitted to our hospital. Her face was pale and painful, indicating a preshock state. No pain was felt in the thyroid gland which was normal in size. The cortisol level was 21 μg/l. T<sub>4</sub> was 156 μg/l, T<sub>3</sub> 2.8 μg/l, fT<sub>4</sub> 47 ng/l and TSH <0.14 mU/l, which indicated thyrotoxicosis. The

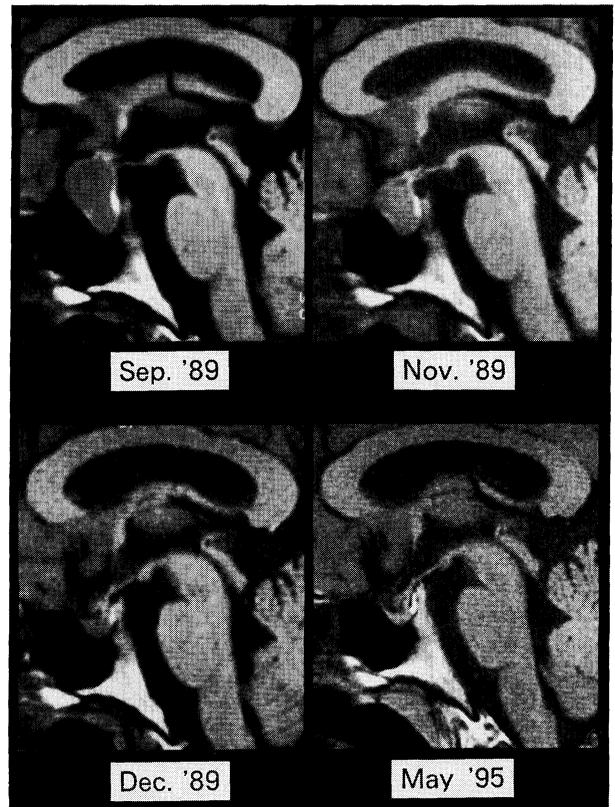


Fig. 1. T<sub>1</sub> weighted MRI revealed a low intensity homogeneous pituitary mass with suprasellar extension in September, 1989, which shrank to its normal size by December, 1989. MRI imaging showed that the pituitary had shrunk to less than one half its normal size by May, 1995 (Case 1).

<sup>99m</sup>TcO<sub>4</sub><sup>-</sup> uptake was only 0.08%. TSH binding inhibitory immunoglobulin was negative. A functional decrease in ACTH-cortisol seemed to have deteriorated due to postpartum painless thyroiditis, resulting in adrenal crisis. Following hydrocortisone administration by intravenous drip infusion, her general condition improved. Anti-GH<sub>3</sub> cell antibody was negative but anti-AtT<sub>20</sub> cell antibody was positive - completely the opposite of the previous results.

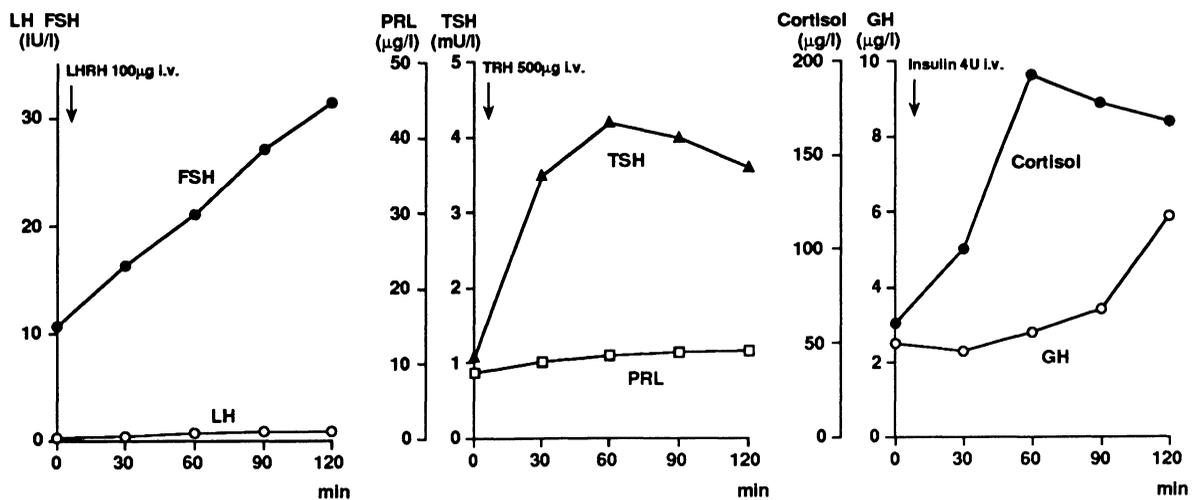
At present she is well managed by oral administration of hydrocortisone at a daily dose of 25 mg. In May, 1995 the basal levels of hormones were as follows: cortisol <10 μg/l; PRL <2.5 μg/l; GH 1.0 μg/l; LH 9.0 IU/l; FSH 6.4 IU/l; TSH 0.7 mU/l and fT<sub>4</sub> 11 ng/l. Cortisol and PRL were extremely low, but others were normal.

Changes in MRI images (Fig. 1): On September

**Table 1.** Time course of endocrinological examination (Case 1)

	Sep. '89	Dec. '89	May '95	Normal range
GH ( $\mu\text{g/l}$ )	1.6	5.9	1.0	<5
PRL ( $\mu\text{g/l}$ )	12	<2.5	<2.5	<30
LH (IU/l)	<0.3	5.1	9.0	0.6–17
FSH (IU/l)	7.8	10.8	6.4	1.6–1.9
ACTH (ng/l)	19			<60
Cortisol ( $\mu\text{g/l}$ )	103	21	<10	50–244
U-17OHCS (mg/day)	2.1	0.9		1.5–8.0
U-17KS (mg/day)	3.1	0.3		2.0–6.0
TSH (mU/l)	1.1	<0.15	0.7	0.5–4.2
fT <sub>4</sub> (ng/l)	5.3	47	11	9.9–15
T <sub>3</sub> ( $\mu\text{g/l}$ )	0.7	2.8	1.3	0.8–2.0
TgAb (%)	30	50		<10
GH <sub>3</sub> Ab	+	–		–
AtT <sub>20</sub> Ab	–	+		–

TgAb, anti-thyroglobulin antibody; GH<sub>3</sub>Ab, anti-GH<sub>3</sub> cell antibody; AtT<sub>20</sub>Ab, anti-AtT<sub>20</sub> cell antibody.

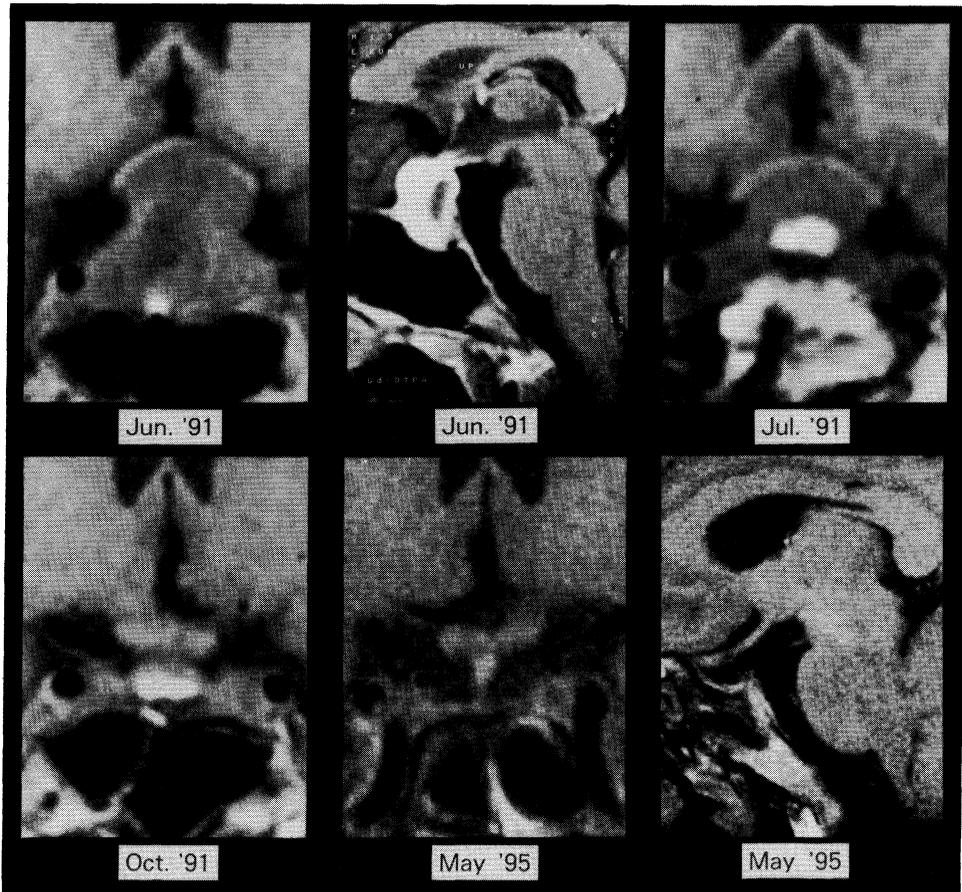
**Fig. 2.** Pituitary function tests two weeks after delivery (Case 1).

8, 1989 (14 days after delivery), the height of the pituitary gland was 22 mm, and it spontaneously decreased to 13 mm by November 6, 1989 (73 days after delivery). Following the administration of massive doses of hydrocortisone on December 18, 1989 (115 days after delivery), a rapid reduction in height was observed and a normal size of 4.9 mm was obtained. On May 29, 1995, six years later, the height further decreased to 2.5 mm, and the optic chiasm dropped to the sella turcica.

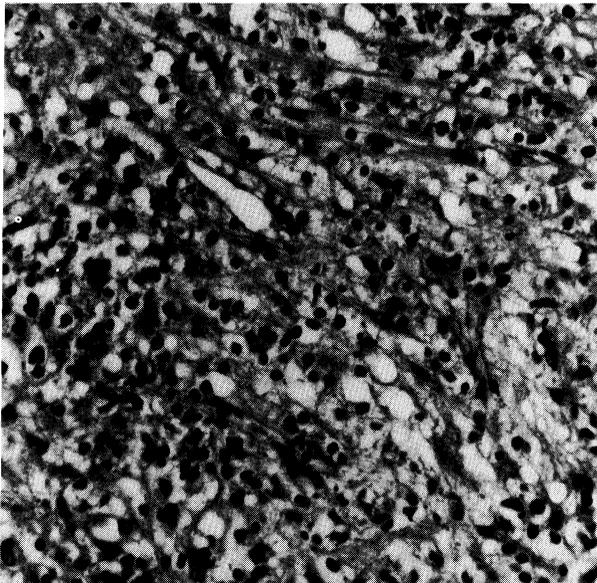
### Case 2

The patient was a 27-year-old woman. In 1991,

when she was 23 years of age, she experienced visual disturbance and headache at nine months of pregnancy. On May 27, 1991, after delivery at 40 weeks, she was admitted to our hospital for workup purposes. No postpartum lactation was observed, but bitemporal hemianopsia was recognized. On June 13, 1991, MRI (Fig. 3) revealed a tumor image extending from the sella turcica to the suprasellar cistern, which showed a lower signal intensity than that of the white matter on T<sub>1</sub>-weighted images. There was also a portion with a low signal within the tumor which in turn was suspected of being a cyst. The posterior lobe of the pituitary gland appeared normal. Transsphen-



**Fig. 3.** T<sub>1</sub> weighted MRI (coronal precontrast and sagittal Gd-DTPA enhanced images) revealed a pituitary mass with cystic lesion in June, 1991. The mass gradually shrank. Serial MRI imaging disclosed marked atrophy of the pituitary gland, which finally showed a finding of empty sella in May, 1995 (Case 2).



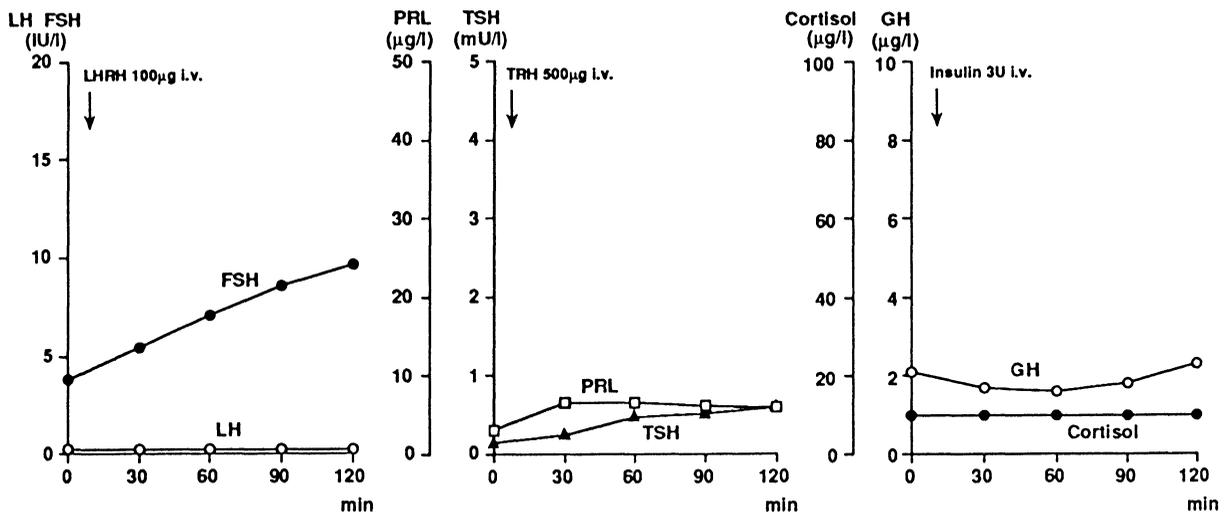
noidal biopsy was scheduled. Pathological examination showed marked infiltration of lymphocytes with extensive fibrosis which indicated lymphocytic adenohypophysitis (Fig. 4). The basal levels of hormones were as follows (Table 2): GH 2.9  $\mu\text{g/l}$ ; PRL <2.5  $\mu\text{g/l}$ ; LH <0.3 IU/l; FSH 3.3 IU/l; ACTH <10 ng/l; cortisol <10  $\mu\text{g/l}$ ; TSH <0.15 mU/l and  $\text{fT}_4$  5 ng/l. LHRH test revealed no response of LH and a delayed response of FSH. TRH test indicated no response of either TSH or PRL. Insulin tolerance test showed no response of either cortisol or GH (Fig. 5). Anti-GH<sub>3</sub> and AtT<sub>20</sub> cell antibodies were negative.

**Fig. 4.** Photomicrograph of the biopsied specimen demonstrates extensive lymphocytic infiltration and interstitial fibrosis (hematoxylin-eosin  $\times 100$ , Case 2).

**Table 2.** Time course of endocrinological examination (Case 2)

	July '91	Dec. '93	May '95	Normal range
GH ( $\mu\text{g/l}$ )	2.9	0.7	0.5	<5
PRL ( $\mu\text{g/l}$ )	<2.5	<2.5	0.6	<30
LH (IU/l)	<0.3	4.3	0.5	0.6–17
FSH (IU/l)	3.3	7.0	6.0	1.6–1.9
ACTH (ng/l)	<10			<60
Cortisol ( $\mu\text{g/l}$ )	<10	<10	<10	50–244
U-17OHCS (mg/day)	0.4			1.5–8.0
U-17KS (mg/day)	0.6			2.0–6.0
TSH (mU/l)	<0.15	1.6	<0.17	0.5–4.2
fT <sub>4</sub> (ng/l)	5	10	17	9.9–15
T <sub>3</sub> ( $\mu\text{g/l}$ )	1.2	1.1	1.4	0.8–2.0
TgAb (%)	8.6			<10
GH <sub>3</sub> Ab	–			–
AtT <sub>20</sub> Ab	–			–

TgAb, anti-thyroglobulin antibody; GH<sub>3</sub>Ab, anti-GH<sub>3</sub> cell antibody; AtT<sub>20</sub>Ab, anti-AtT<sub>20</sub> cell antibody.

**Fig. 5.** Pituitary function tests two weeks after delivery (Case 2).

Clinical course and changes in endocrinological data are also shown in Table 2. Administration of hydrocortisone at 25 mg/day and levothyroxine at 50  $\mu\text{g/day}$  was begun for the treatment of hypopituitarism. Bitemporal hemianopsia gradually improved and was finally resolved two months after delivery. The patient's general condition improved, and there were menstruations at three-month intervals. Endocrinological studies on replacement treatment in December, 1993 showed that LH (4.3 IU/l), FSH (7.0 IU/l), TSH (1.6 mU/l) and fT<sub>4</sub> (10 ng/l) were normal, whereas GH (0.7  $\mu\text{g/l}$ ), PRL (<2.5  $\mu\text{g/l}$ ) and cortisol (<10  $\mu\text{g/l}$ ) were low.

The patient delivered her second child on May 8, 1995. She had a normal visual field shortly before delivery. The endocrinological data on replacement treatment after delivery were very similar to those obtained in July, 1991. ACTH, PRL, GH and TSH were markedly low throughout the entire clinical course.

Changes in MRI images (Fig. 3): On June 13, 1991 (17 days after her first delivery), the height of the pituitary gland was 23mm. On July 10, 1991 (44 days after delivery) it gradually decreased to 17 mm, and returned to a normal size of 5.5 mm on October 2, 1991 (128 days after delivery). On May 12, 1995, immediately after the delivery of

her second child on May 8, 1995, it markedly shrank to approximately 1 mm, which indicated empty sella.

### Discussion

Changes in the pituitary gland were serially observed by MRI in two cases of lymphocytic adenohypophysitis. In both cases, the pituitary gland which had swollen during the late stage of pregnancy of the first child gradually decreased to a normal size 3 or 4 months after delivery. In case 1, the swollen pituitary gland rapidly shrank following administration of massive doses of hydrocortisone for the treatment of acute adrenal insufficiency induced by thyrotoxicosis caused by painless thyroiditis. Six years later, the pituitary gland became so atrophic that the optic chiasm dropped to the sella turcica. In case 2, the patient became pregnant with her second child four years later, but there was no visual field defect during pregnancy, and MRI studies immediately after delivery revealed empty sella. During pregnancy, the pituitary gland did not swell and remained atrophied.

In addition to surgery, irradiation and drug therapy on pituitary adenoma, the well-known causes of secondary empty sella include pituitary infarction and hemorrhage [5]. In particular, hypopituitarism due to pituitary infarction developing after delivery is called Sheehan's syndrome. In cases of Sheehan's syndrome, many are found to have empty sella several years to some ten years after delivery rather than immediately after delivery. For this reason, lymphocytic adenohypophysitis-induced empty sella may be included in cases of established Sheehan's syndrome associated with empty sella [6]. Patients with empty sella have a high prevalence of anti-pituitary antibody [7]. Komatsu *et al.* [8] reported that of 32 patients with empty sella, 24 (75%) were positive for anti-AtT<sub>20</sub> cell antibody, and 15 (47%) for anti-GH<sub>3</sub> cell antibody. The clinical significance of these two antibodies has yet to be elucidated because some cases of pituitary adenoma and autoimmune thyroiditis also are positive for them [9, 10]. These antibodies have been detected in many patients with lymphocytic adenohypophysitis [2, 11–13], which is thought to be an autoimmune disease. It is believed that lymphocytic adenohypophysitis

may be closely related to empty sella.

Most patients with hypopituitarism developing after delivery used to be diagnosed as having Sheehan's syndrome. In recent years, the number of lymphocytic adenohypophysitis cases has been increasing [2–4]; thus, lymphocytic adenohypophysitis is considered to be one of the causes of postpartum hypopituitarism [11, 14]. In case 1, ACTH and PRL decreased, while in case 2, GH and TSH, as well as ACTH and PRL, decreased. In reported cases of lymphocytic adenohypophysitis, a decrease in ACTH is most prevalent, followed by decreases in PRL and GH. There are some cases of panhypopituitarism involving LH, FSH and TSH [2, 15]. There are cases, though limited in number, of normal pituitary function [16]. Several cases have been reported to be complicated with diabetes insipidus [17]. At the same time, differential diagnosis of lymphocytic adenohypophysitis and lymphocytic infundibuloneurohypophysitis [18] should be made in future. Selective loss of adenohypophysial cells is likely to be the result of a targeted autoimmune attack during late pregnancy or in the postpartum period. In case 1, serum ACTH and cortisol levels were normal immediately after delivery, and anti-AtT<sub>20</sub> cell antibody was negative. Later, however, anti-AtT<sub>20</sub> cell antibody became positive, and ACTH and cortisol gradually decreased and then dropped below the detection limits. Since the administration of massive doses of steroid in case 1 was effective in decreasing the size of the swollen pituitary gland, steroid therapy is likely to prevent the onset of hypopituitarism and should therefore be evaluated in future for the early treatment of lymphocytic adenohypophysitis.

In case 1, lymphocytic adenohypophysitis developed during late in pregnancy. Pituitary antibody was positive. MRI studies indicated symmetrical swelling of the pituitary gland with a low-signal intensity on T<sub>1</sub> weighted images, a high-signal intensity on T<sub>2</sub> weighted images, and homogeneity on Gd-DTPA contrast images. The patient was clinically diagnosed as having lymphocytic adenohypophysitis. Those MRI findings are therefore thought to be representative of lymphocytic adenohypophysitis [19]. In case 2, since MRI could not rule out pituitary adenoma because of the heterogeneous intensity of the swollen pituitary gland, biopsy was performed to confirm lymphocytic adenohypophysitis. Pathological findings were

characterized by infiltration of lymphocytes with extensive fibrosis, which was compatible with lymphocytic adenohypophysitis. Biopsy was considered to be essential for the diagnosis of lymphocytic adenohypophysitis, but since representative cases of lymphocytic adenohypophysitis such as case 1 were easy to diagnose, one should be extremely prudent when performing biopsy for the diagnosis of lymphocytic adenohypophysitis. Ahmadi *et al.* [20] suggested that biopsy may be needed to establish the correct diagnosis only when a trial of steroid therapy fails.

As described previously, the histological appearance of lymphocytic adenohypophysitis is strikingly similar to that of chronic thyroiditis [21]. In the diagnosis of chronic thyroiditis, palpation and imaging findings are extremely diverse, ranging from huge goiters to unlimitedly atrophied organs. As far as we know there were no cases in

which a pituitary gland mass persisted for several years. It is presumed that during the period of pregnancy when the pituitary gland swells, the pituitary gland exhibits an antigenicity, triggers an autoimmune reaction, and produces a mass resembling chronic thyroiditis. This tumor shrinks after delivery and is subsequently atrophied. It is not yet clear what major factors intervene in the tumor formation and/or atrophy of the pituitary gland.

The long-term clinical course of lymphocytic adenohypophysitis was observed by diagnostic methods including MRI. It is believed that some of the classic cases of Sheehan's syndrome associated with empty sella include lymphocytic adenohypophysitis [4, 6, 22]. It is essential to clearly make a differential diagnosis of lymphocytic adenohypophysitis and Sheehan's syndrome.

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