EMPTY SELLA MAY BE THE FINAL OUTCOME
IN LYMPHOCYTIC HYPOPHYSTIS

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□ Introduction. Lymphocytic hypophysitis (LH) is an autoimmune disorder associated with the
infiltration of the pituitary gland by lymphocytes leading to different degrees of hypopituitarism.
Females are affected more frequently than males and the disease is usually associated with pregnancy or
postpartum period. Case. We present a case of LH who was first diagnosed with diabetes insipidus
and hyperprolactinemia. In the follow-up, the patient developed growth hormone, gonadotropin,
and thyroid stimulating hormone deficiency. The typical appearance of increased stalk thickness
and diffuse homogenous contrast enhancement of pituitary on magnetic resonance imaging
resulted in empty sella by time. Conclusion. The present case demonstrates the natural course of
LH over a 13-year period in which the empty sella was the final outcome.

Keywords Lymphocytic Hypophysitis, Empty Sella

INTRODUCTION

Lymphocytic hypophysitis (LH) is an autoimmune disorder characterized by lymphocytic infiltration and destruction of the pituitary gland leading to various degrees of pituitary dysfunction (1). LH can be associated with other autoimmune disorders, especially with autoimmune thyroid disorders such as Hashimoto thyroiditis and, rarely, Graves’ disease (2). Based on the
anatomical location, LH can be classified as lymphocytic adenohypophysitis (LAH), lymphocytic infundibuloneurohypophysitis (LINH), and lymphocytic panhypophysitis (LPH). LAH, which usually manifests during pregnancy or postpartum period, is more common in females. LINH affects males and
females equally and LPH is slightly more common in females (3). LAH is

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characterized by anterior pituitary dysfunction, usually adrenocorticotropic hormone (ACTH) being the first hormone to be lost. LINH is characterized clinically by diabetes insipidus (DI) and diffuse thickening of the pituitary stalk and, usually, loss of neurohypophysial “bright spot” in the imaging studies. LPH involves both anterior and posterior pituitary (1). Diagnosis of LH is pathological, but imaging studies, especially pituitary magnetic resonance imaging (MRI), are also very useful in diagnosis. There are no prospective data for MRI findings of LH resulting eventually in empty sella. The present case demonstrates the natural course of LH over a 13-year period in which the empty sella was the final outcome.

CASE

The patient was a 37-year-old woman who had been admitted to another hospital 13 years ago with the complaints of polyuria (10–12 L/day) and polydipsia. The patient was started on bromocriptine and desmopressin nasal spray because of symptomatic hyperprolactinemia and DI. The pituitary MRI revealed an appearance compatible with LINH (Figure 1), but the data regarding hormonal evaluation on first admission were not available. The patient had regular menses for a couple of months and bromocriptine was discontinued.

Three years later, the patient gave birth to a child and one year after parturition she was admitted to Erciyes University Department of Endocrinology with galactorrhea and amenorrhea. On admission, she was asymptomatic for DI with desmopressin nasal spray. Clinically, the patient had hyperprolactinemia, DI, and gonadotropin deficiency (Tables 1, 2, and 3). Bromocriptine and estrogen replacement therapy were commenced.

When she was admitted 13 years after the diagnosis with the complaints of fatigue and amenorrhea, the patient was on bromocriptine and desmopressin therapy. GH, gonadotropin, and thyroid stimulating hormone (TSH) deficiencies were detected (Tables 1 and 2). Desmopressin was discontinued for 2 days and urine volume increased up to 11 L/day. Morning first void urine osmolality was 62 mOsm/kg and serum osmolality was 306 mOsm/kg, which were compatible with DI. The pituitary MRI revealed an appearance of empty sella (Figure 2A and 2B).

The patient was started on levothyroxine (50 μg/day), desogestrel 150 μg, and ethynylestradiol 20 μg combination. Desmopressin was continued for DI.

DISCUSSION

LH is an autoimmune disease that affects females more frequently than males and mean age at diagnosis being 34.5 years for females and 44.7 years for males (4). In females, LH is usually associated with pregnancy or postpartum
FIGURE 1 (A) The precontrast sagittal section of pituitary MRI demonstrates thickened pituitary stalk and loss of "bright spot" of neurohypophysis. (B) Diffuse homogenous contrast enhancement of the pituitary.
TABLE 1 Serum Levels of Basal Hormones

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<tr>
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<th>4 years after diagnosis</th>
<th>13 years after diagnosis</th>
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<tr>
<td>ft3 (2.2–4.7 pg/mL)</td>
<td>2.03</td>
<td>2.51</td>
</tr>
<tr>
<td>ft4 (8–20 pg/mL)</td>
<td>8.4</td>
<td>7.73</td>
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<tr>
<td>TSH (0.2–3.2 μU/mL)</td>
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<td>0.3</td>
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<tr>
<td>FSH (2.5–12.5 mIU/mL)</td>
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<td>LH (1.9–12.5 mIU/mL)</td>
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<td>0.18</td>
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<td>Estradiol (11–69 pg/mL)</td>
<td>23.9</td>
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<tr>
<td>ACTH (5–60 pg/mL)</td>
<td>97</td>
<td>59</td>
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<td>F (9.41–26 μg/dL)</td>
<td>21.5</td>
<td>16.48</td>
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<tr>
<td>PRL (2.8–29 ng/mL)</td>
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<tr>
<td>IGF-1 (107–310 ng/mL)</td>
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TABLE 2 GH and Cortisol Responses to Insulin Tolerance Test (ITT)

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<td>4 years later</td>
<td>16.3</td>
<td>30.8</td>
<td>25.2</td>
<td>18.4</td>
<td>16.3</td>
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<tr>
<td>Cortisol (μg/dL)</td>
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<tr>
<td>13 years later</td>
<td>11.5</td>
<td>15.97</td>
<td>13.64</td>
<td>8.15</td>
<td>7.93</td>
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<tr>
<td>4 years later</td>
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<td>0.01</td>
<td>0.05</td>
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<tr>
<td>GH (μIU/mL)</td>
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<td>0.16</td>
<td>0.11</td>
<td>0.05</td>
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TABLE 3 FSH and LH Response to GnRH, TSH, and PRL Response to TRH Stimulation Tests in 1998 (4 years after diagnosis)

<table>
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<tr>
<td>FSH (μIU/mL)</td>
<td>2.79</td>
<td>6.22</td>
<td>5.73</td>
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<td>LH (μIU/mL)</td>
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<td>0.31</td>
<td>1.07</td>
<td>1.01</td>
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<tr>
<td>TSH (μIU/mL)</td>
<td>0.98</td>
<td>8.53</td>
<td>7.87</td>
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<td>PRL (ng/mL)</td>
<td>41.82</td>
<td>55.94</td>
<td>60.53</td>
<td>56.6</td>
<td>58.41</td>
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period (5,6) The present case with LH was a woman diagnosed at age 25 years without an associated pregnancy. On the first admission, clinical presentation was DI and hyperprolactinemia, which are characteristics of LINH. Hyperprolactinemia affects about one-third of patients with LH. Several causes have been suggested for hyperprolactinemia; stalk compression or inflammatory process itself altering inhibitory effect of dopamine on prolactin (PRL) or release of hormones into bloodstream from destructed tissue or PRL stimulating antibodies (7,8,9). The pituitary MRI of the patient was characteristic for LINH with diffuse thickening of the pituitary stalk, enhanced contrast enhancement of the gland, and loss of neurohypophyseal “bright spot” as described in the literature (10,11). Diagnosis of LH is difficult; it can be easily mistaken for a pituitary adenoma and referred for surgery (12). Symmetrical
FIGURE 2 (A) The postcontrast coronal section. (B) The postcontrast sagittal section of pituitary MRI demonstrates empty sella.
pituitary enlargement, thickened stalk without deviation, uniformly flat sellar floor, appearance of dural tail, and loss of "bright spot" of neurohypophysis are the clue findings for differentiation from pituitary adenoma (4). In the present case all were found, but dural tail, which represents the contrast enhancement of dura adjacent to pituitary, was not. The age, sex, clinical presentation, and the imaging studies have all suggested LH. Unfortunately antipituitary antibodies were unavailable, which are also suggestive for LH (1). Definitive diagnosis of LH requires histopathological examination, but due to lack of visual disturbances or mass effect surgery was not performed.

One year after parturition, besides DI and hyperprolactinemia, GH and gonadotropin deficiency were also detected. Although spontaneous resolution has been reported for LH (13), ongoing tissue destruction may eventually lead to variable degrees of pituitary dysfunction (4). Postpartum presentation of amenorrhea without obstetric hemorrhage and failure of lactation, associated DI with hyperprolactinemia, and imaging findings helped to rule out Sheehan's syndrome. ACTH is usually the first hormone lost in LH patients with isolated hormone deficiency (14), but not in this case.

Thirteen years after the diagnosis, the patient was reevaluated and DI, TSH, GH, and gonadotropin deficiencies were present. Cortisol response to the insulin tolerance test (ITT) was subnormal, which could be presumptive for ACTH deficiency in the future. The pituitary MRI revealed empty sella. LH is usually associated with other autoimmune diseases (1,2), but no autoimmune diseases could be detected clinically.

The course of LH is not well known. Empty sella associated with LH confirmed by histopathological diagnosis of LH was first reported by Unluhizarci et al. (15). Matta et al. (16) reported an interesting case of a recurrent LH mimicking aseptic meningitis followed for about 9 years who developed partial empty sella. But the patient was treated with high dose glucocorticoid, which might be responsible for shrinkage of the pituitary gland. In other words, natural course of LH in that case was affected by glucocorticoid treatment. Ishihara et al. (17) reported two cases with LH who developed empty sella. But the development of empty sella was not due to the natural course of LH. In one of the patients massive doses of hydrocortisone were administered, which resulted in a rapid reduction in pituitary height. In the other patient, transsphenoidal biopsy, which may damage the pituitary tissue, was performed and hydrocortisol at 25 mg/day was administered. Although the dosage of hydrocortisone was not pharmacological, it may also affect the natural course of LH. On the other hand, the patient developed empty sella immediately after the delivery of her second child.

The data about the effects of glucocorticoids on LH in terms of radiological changes are also limited. Gagneja et al. (18) described a patient with histologically proven LH, in whom the pituitary mass regressed completely with physiological hydrocortisone therapy. Reusch et al. (19) tried a short course
of dexamethasone in a pregnant woman because of visual field defects due to a pituitary mass. The patient underwent partial hypophysectomy for decompression, since there was a rapid progression of visual field defects while the patient was on glucocorticoid therapy and the pathology confirmed the diagnosis of LH. The dosage and duration of steroids were thought to be ineffective. Kristof et al. (20) reported their findings and courses of nine patients with LH treated with high dose methylprednisolone therapy. Shrinkage of the sellar mass or pituitary stalk was reported on MRI of seven patients, varying from a slight degree of shrinkage to nearly an empty sella in one of the patients whose diagnosis was confirmed by transsphenoidal biopsy. Two of the patients had transsphenoidal biopsy, one of them associated with nearly an empty sella and one patient underwent complete removal of the pituitary mass.

Association of empty sella with LH is reported in a limited number of cases that were suspected by the presence of antipituitary antibodies (21–24). Pituitary antibodies may be helpful for suspected cases. But it has also been reported that autoimmunity per se may not be significantly linked to the occurrence of primary empty sella (25). Hashimoto et al. (26) followed six patients with isolated TSH deficiency owing to LH, and MRI of the pituitary gland was taken at the beginning and at the end of the study period of 31–60 months. Empty sella was detected in only one patient at the beginning.

Empty sella may be the final outcome of LH, and, at this stage, exact diagnosis is usually impossible. The patient with pituitary insufficiency and empty sella, especially when associated with pregnancy and postpartum period, may be misdiagnosed as Sheehan’s syndrome. This case is important since the clinical presentation and imaging was strongly suggestive for LH, and, in the follow-up, the typical appearance of LH resulted in empty sella.

The present case is a representative example for the natural course of LH in which empty sella was the final outcome. The course of the patient demonstrates both the changes in pituitary imaging and progressive loss of pituitary functions by time. LH should be kept in mind in patients with empty sella, hyperprolactinemia, and pituitary insufficiency.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

REFERENCES

field defects due to increased intracranial pressure may be encountered, especially when the patient is not vomiting, and the diagnosis of Cushing's syndrome is likely to be ineffective. Endocr Rev 2005; 26:599–614.


