CASE REPORT

Lymphocytic Hypophysitis Causing Hypopituitarism and Diabetes Insipidus, and Subsequent Association With Primary Autoimmune Hypothyroidism and Type 1 Diabetes Mellitus, in a Nonpregnant Female With Complete Recovery of Pituitary Function and Pregnancy

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Abstract: We describe a case of lymphocytic hypophysitis (LYH) in a 25-year-old nulliparous woman who presented with marked lethargy, profound tiredness, weight gain, postural hypotension, and visual disturbance. Endocrine investigations revealed low thyroid stimulating hormone, low T4, and high prolactin levels. Her CT scan revealed a macroadenoma with suprasellar extension, encroaching on the optic chiasm. In view of visual disturbance and clinical hypopituitarism, transphenoidal resection of the tumor was performed and normal-looking pituitary tissue was preserved. Histology revealed LYH. During postoperative period, she developed diabetes insipidus followed by type 1 diabetes mellitus and autoimmune primary hypothyroidism. Over a period of 3 years, her pituitary function completely recovered. Subsequently she had 2 successful pregnancies. She has been followed for 10 years with no recurrence of LYH. The recovery of pituitary function in LYH and subsequent successful pregnancies as well as the association with diabetes insipidus and primary autoimmune thyroiditis are recognized. The association with type 1 diabetes mellitus, however, is unusual. This case highlights the importance of careful follow up because spontaneous remission of pituitary hormone deficiencies and the emergence of other autoimmune diseases can occur.

Key Words: lymphocytic hypophysitis, type 1 diabetes mellitus, pregnancy, autoimmune hypothyroidism, diabetes insipidus

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Since the first description of lymphocytic hypophysitis (LYH) by Goudie and Pinkerton1 in a postmortem case and by Quencer2 in a living patient in 1980, many reports of LYH have been published, which review its diagnosis, autoimmune basis, and clinical course.3 Although it is considered primarily a disease of women in late pregnancy and postpartum period, cases in nonpregnant women4–6 and men8,9 have also been reported.

Clinically, it is characterized by a compressive suprasellar mass associated with isolated or multiple anterior pituitary hormone deficiencies. Corticotrophin secretion is most frequently impaired, whereas prolactin secretion is least disturbed. Involvement of neurohypophysis is unusual but infundibulo-neurohypophysitis has been reported.10,11 Histologically, the anterior pituitary gland is extensively infiltrated by lymphocytes, plasma cells, and macrophages. T lymphocytes (CD4) are more numerous than B lymphocytes. Lymphoplasmacytic aggregates surround atrophic acini of pituitary cells, and the remaining pituitary tissue shows areas of reactive fibrosis.12–15 Twenty-five percent of these patients have an association with other autoimmune disorders16 such as autoimmune thyroiditis, atrophic gastritis, pernicious anemia, lymphocytic parathyroiditis, and adrenalitis.1,5,17–19 Organ-specific antibodies, including antipituitary antibodies, antimitochondrial antibodies, antiparietal cell antibodies, and antinuclear antibodies, are present in selected cases.18–20

We present a nulliparous woman who presented with partial hypopituitarism; histologic examination revealed LYH. She subsequently developed diabetes insipidus, insulin-dependent diabetes mellitus, and autoimmune hypothyroidism. With time, her pituitary function has completely recovered and she has managed to conceive and deliver 2 normal children. Both pregnancies were uncomplicated and there was no recurrence of LYH.

CASE REPORT

A 25-year-old nulliparous nurse was referred in April 1995 to our endocrine center with a 1-year history of feeling “light headed” on standing, and symptoms suggestive of hypoglycemia, which were relieved by taking sugar. There was a 2-year history of a cold intolerance. She complained of lethargy, weight gain (14 kg), constipation, and slow dysarthric speech. A few weeks before coming to our clinic, she had experienced blurring of vision and a central headache. There was no history of galactorrhoea. She had been taking
oral contraceptive pills for 6 years. She was not taking any other regular medication. There was no significant medical history and no family history of endocrine disorder, diabetes mellitus, or autoimmune disease.

Physical examination revealed an overweight lady with waxy, pale skin. She appeared grossly hypothyroid with scanty secondary sexual characteristics (both axillary and pubic hair were diminished). Postural hypotension was noted. Her visual acuity and visual fields were normal and there was no evidence of raised intracranial pressure. She was treated with hydrocortisone, 20 mg morning and 10 mg evening, and 3 days later she was given thyroxine, 50 μg per day. The symptoms began to improve with hydrocortisone and thyroxine replacement.

A full blood count, erythrocyte sedimentation rate, C-reactive protein, electrolytes, kidney and liver function tests, and blood glucose were normal. Thyroid stimulating hormone (TSH) 0.32 mU/L (reference range: 0.2–4.5) was low as was free thyroxine (FT4) 1.5 pmol/L (reference range: 10–24). Follicle-stimulating hormone (FSH) was 3.9 U/L (reference range: 1.0–7.0 U/L), and LH was 4.7 U/L (reference range: 1.0–8.0 U/L). Prolactin was high at 1123 mU/L (reference range: <450). A pituitary CT scan revealed a large macroadenoma that filled the sella with a suprasellar extension to the optic chiasm.

She was referred for transphenoidal resection of the pituitary tumor. A fairly extensive lesion was removed up to the sella diaphragm. Some normal-looking pituitary tissue was preserved. She developed polydipsia and polyuria in the postoperative period and a diagnosis of diabetes insipidus was made. Treatment with DDAVP (desmopressin) nasal spray was commenced, which led to normalization of serum electrolytes and osmolality.

During the first 2 weeks after surgery she developed hyperglycemia, which could not be controlled by diet alone. She was started on an oral hypoglycemic agent (Gliclazide). Within 3–4 weeks, she developed ketonuria. Antipancreatic islet cell antibody was positive and diagnosis of type 1 diabetes mellitus was established. She was started on insulin therapy and had good diabetic control. Along with insulin she was continued on thyroxine 100 μg, Hydrocortisone 30 mg a day, DDAVP, and combined oral contraceptive pill.

The histology showed no evidence of pituitary adenoma or granuloma. Immunocytochemical staining revealed infiltration of T cells but no B cells and moderate number of macrophages. The T cell infiltrate was diffuse with no aggregation. There was no evidence of necrosis. The picture was highly suggestive of adenohypophysitis with lymphocytic infiltrate/LYH.

As LYH can be associated with other autoimmune disease, further immunologic investigations such as antinuclear, antimitochondrial, antiparietal cell antibodies, and autoantibodies against adrenal cortex were carried out and were all negative.

**Subsequent Course**

The patient improved symptomatology. Prolactin fell to the normal range immediately postoperatively and remained normal throughout the follow-up period.

<table>
<thead>
<tr>
<th>Time (hr:min)</th>
<th>BI Glucose (mmol/L)</th>
<th>S. Cortisol (nmol/L)</th>
<th>GH (mU/L)</th>
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<td>7.4</td>
<td>631</td>
<td>5.8</td>
</tr>
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<td>2.5</td>
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<td>1.8</td>
</tr>
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<tr>
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<tr>
<td>11:55</td>
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<td>14.7</td>
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Two months postoperatively, thyroid peroxidase antibody level increased to 21 mU/L and T4 increased to 13 pmol/L despite the patient taking thyroxine 100 μg once a day. The TPO antibody titer was 170 U/L (reference range: 0–100) suggesting diagnosis of primary hypothyroidism of autoimmune origin. Further endocrine testing revealed FSH of 2.7 U/L and a LH of 2.1 U/L. There was a blunted response of serum cortisol to Cortrosyn. Baseline S cortisol was 136 nmol/L (reference range: 150–650 nmol/L) rising to 149 nmol/L at 60 minutes. She was continued on hydrocortisone, thyroxine, insulin, oral contraceptive pill, and DDAVP.

Serum FSH and LH levels started to rise slowly postoperatively, and patient’s requirement of hydrocortisone seemed to fall. An insulin stress test (Table 1) revealed adequate cortisol reserve. Hydrocortisone was completely stopped 28 months postoperatively. An attempt to reduce thyroxine replacement was accompanied by the clinical symptomatology of hypothyroidism along with an increase in serum TSH. Thyroxine replacement was continued.

With time, DDAVP was reduced to single administration at night. Three years after initial presentation, DDAVP was completely stopped. Repeat dynamic function test continued to show adequate cortisol and GH response, and for the first time, luteinizing hormone-releasing hormone test revealed adequate gonadotrophin reserve.

Four years after the surgery the patient wished to start a family and discontinued oral contraceptive pills. Within 6 months she conceived naturally. During pregnancy, hypothyroidism and diabetes mellitus were managed with thyroxine and insulin. She was closely followed throughout the pregnancy and she delivered a healthy baby. Follow-up brain scan showed signals of normal pituitary gland with no evidence of tumor recurrence.

Seven years after initial presentation, she became pregnant for the second time and delivered another healthy baby. There was no evidence of any other endocrine disturbance or recurrence of LYH.

**DISCUSSION**

Our patient had a long history of endocrine dysfunction, suggested by her symptoms and somatic features. We believe her mild hypogonadism was masked by withdrawal bleeding, induced by the contraceptive pills. Her initial presentation, along with low T4 and TSH levels, was highly suggestive of partial hypopituitarism.
The finding of increased prolactin at diagnosis is unusual in LYH. Increase in serum prolactin in our patient could be because of stalk compression resulting in decreased dopamine delivery to the anterior pituitary (stalk section phenomenon). Alternatively, diffuse destruction by inflammatory process might have resulted in escape of prolactin hormone in circulation. Postoperatively, improvement in the hyperprolactinemia could be related to the surgery itself or correction of hypothyroidism with adequate replacement, as hyperprolactinemia can be seen with hypothyroidism due to TRH stimulatory effect on prolactin.

Diabetes insipidus in this woman became evident after surgery and could be related to the surgery. However, the decreasing need for DDVAP and improvement in patient symptomatology indicate that this could also be part of the inflammatory process involving the neurohypophysis.

After surgery, there was gradual improvement in the pituitary function, and her TSH level started increasing. The presence of positive thyroid antibodies and persistent dependency on exogenous thyroxine were indicative of primary autoimmune hypothyroidism, which is a recognized association with LYH. The clinical picture, together with CT appearance suggestive of large pituitary adenoma encroaching on the chiasma, led to urgency in treating this patient with steroids. This may have had some impact on the overall outcome and could have been an explanation for the appearance of diabetes mellitus. The patient was prescribed 30–40 mg of hydrocortisone for replacement, which may have precipitated diabetes mellitus. Failure to control blood sugars with oral hypoglycemic agents, development of ketosis, and presence of islet cell antibodies indicate the insulin-dependent nature of her diabetes. This is an extremely unusual case of LYH associated with both type 1 diabetes and autoimmune hypothyroidism.

The role of imaging in LYH is particularly important for accurate diagnosis. In LYH, the lesion generally appears as a symmetrical mass affecting the entire gland with thickened stalk and suprasellar extension displacing the optic chiasma. The sella floor is usually flat with no evidence of destruction. After injection of gadolinium, pituitary enhancement is homogenous with a strip of enhanced tissue along the dura madre (so-called “dural tail”). All these features favor diagnosis of diffuse inflammatory pituitary infiltrate of LYH. In contrast, pituitary adenomas are usually associated with asymmetric pituitary enlargement with deviation of stalk and there may be unilateral destruction of the sellar floor.

Several reports of spontaneous recovery or remission after steroid treatment with subsequent resumption of fertility and pregnancy suggest trial of steroids if LYH is the most likely diagnosis. In our patient, the relative scarcity of LYH infiltrate and lack of further destruction of the pituitary gland could also be related to steroid treatment. Improvement with smaller doses of steroids has been reported although much higher doses were required to achieve an anti-inflammatory effect.

In our patient, as well as other cases reported in the literature, pituitary biopsy or partial resection of abnormal-looking pituitary is both diagnostic and therapeutic, and progressive recovery of pituitary function can be observed. However, in patients with symptoms or signs of severe compression, surgical transphenoidal resection with an intrasurgical cytotastic slide can confirm the diagnosis and save possible viable pituitary tissue.

The association of LYH with autoimmune diseases suggests that type 1 diabetes could also be linked in predisposed individuals. Human leukocyte antigens DR4, DR5, DRW53/52, and DQW3 are detected in patients with Hashimoto thyroiditis whereas HLA-BW35 and A28 are associated with insulin-dependent diabetes mellitus. All these human leukocyte antigen (HLA) antigens, including DR3,12,21,27 have also been detected in patients with LYH. The presence of these specific subtypes of major histocompatibility complex HLA may predispose patients, mainly whites, to the development of thyroiditis, insulin-dependent diabetes mellitus and, less commonly, antipituitary antibodies, and the emergence of LYH.

Recovery of the pituitary-adrenal and gonadal axis in our patient and the restoration of pituitary reserve of TSH, add to the previous reports on recovery of pituitary function. In such cases, hypopituitarism may have been caused by compression of hypophyseal cells either by inflammatory infiltrate or edema, rather than by irreversible cell destruction.

The diagnosis of LYH should be considered in all women of childbearing age who present with pituitary mass and in those patients in whom pituitary hormone deficiency is noted in association with a coexisting autoimmune disorder.

CONCLUSION

We reported a case with LYH presenting with hypopituitarism. It was associated with subsequent development of diabetes insipidus, type 1 diabetes mellitus, and primary autoimmune hypothyroidism. The patient now has complete recovery of pituitary function and 2 successful pregnancies without recurrence of LYH. Although subsequent successful pregnancies have been reported in patients with LYH, to our knowledge this is an unusual case of LYH showing association with type 1 diabetes mellitus. We recommend a careful follow up in these patients because spontaneous remission of pituitary hormone deficiencies, emergence of other autoimmune disease or rarely late recurrence can occur.

REFERENCES

6. Duran Martinez M, Santonja C, Pavon de Paz I, et al. Lymphocytic...


