Suspected lymphocytic hypophysitis in a man

Elham Reda

Lymphocytic hypophysitis is a rare but increasingly recognised inflammatory disease, considered to be autoimmune. It can involve the anterior and/or posterior lobe of the pituitary gland with corresponding hormone deficiencies. Most cases occur in women, mainly during late pregnancy or the early postpartum period. The diagnosis can be challenging in many cases, because distinction from pituitary adenomas and other sellar masses is not obvious. The therapeutic approach is controversial and, although transphenoidal surgery is often performed, a conservative medical management is justified in many cases, given the self-limited nature of the inflammatory process.

We describe a 36-year-old man who was acutely admitted to our hospital because of acute confusion. Cerebrospinal fluid (CSF) analysis showed lymphocytic pleocytosis and negative viral serology. Magnetic resonance imaging (MRI) demonstrated an enlarged pituitary gland with homogeneous enhancement, post contrast. The endocrinologic data indicated impaired secretion of ACTH and gonadotropin, associated with thyroiditis.

Together, the findings strongly suggested a diagnosis of lymphocytic hypophysitis. He was managed nonoperatively, with glucocorticoid replacement, and his symptoms dramatically reduced.

The present case highlights the fact that surgical intervention is not always necessary in suspected cases of lymphocytic hypophysitis. Careful and considered clinical judgment is required in the management of these patients.

Case report

A 36-year-old white man was admitted to hospital with a history of general fatigue, weakness, nausea, vomiting, and dizzy spells of 1 month duration. He also complained of lack of appetite and weight loss of 20 kg. He described mild morning frontal headaches, often relieved with paracetamol. He denied having visual disturbances, abdominal pain, decreased potency, or polyuria. Slowing of intellectual functions and loss of concentration were also noted.

The patient had no significant prior medical history and no family history of diabetes, thyroid, or autoimmune problems.

Physical examination revealed a well-developed man, though apathetic and slow to answer. He was afebrile with no meningism or skin rash. There was no postural hypotension and the thyroid gland was normal to palpation. Neurological examination was normal with normal visual fields and optic discs. The remaining examination was otherwise unremarkable.

Cerebrospinal fluid (CSF) pressure was increased and analysis showed lymphocytic pleocytosis (leucocytes 288 ×10⁶/L, 98% lymphocytes), elevated protein.
concentration (1.11g/L), and negative cultures. Meningococcal DNA and herpes simplex virus RNA were not detected by nucleic acid amplification.

According to a basic laboratory evaluation, full blood count, serum creatinine and electrolyte levels, plasma glucose, and liver function indices were all normal. C-reactive protein was mildly elevated. Blood cultures showed no growth. Initial endocrinological evaluation revealed secondary hypocortisolism and hypogonadism; thyroiditis; but no other evidence of pituitary hormone hypersecretion.

Plasma adrenocorticotropin hormone (ACTH) was <1 pmol/L (normal range [NR] 2.0–11.0). Basal serum cortisol was <10 nmol/L with increase to 92 at 30 minutes and 150 nmol/L at 60 minutes after administration of 0.25 mg synthetic ACTH. Dehydroepiandrosterone sulphate (DHEA-S) was <0.4 umol/L (NR 3.2–14.1).

Gonadotrophic function was also depressed, with a serum follicle stimulating hormone (FSH) level of 0.5 U/L (NR 1.0–14.0), serum luteinizing hormone (LH) level of <0.2 U/L (NR 1.0–10.0), and a serum testosterone level of <0.4 nmol/L (NR 9.0–30.0). Serum prolactin was <50 mIU/L (NR 0.0–360), and GH (growth hormone) 1.4 ug/L (NR 0.0–4.1).

Serum thyroid stimulating hormone (TSH) 0.01 mU/L (NR 0.3–4.0), serum free thyroxin (FT4) 43 pmol/L (NR 10–20), serum free triiodothyronin (FT3) 22 pmol/L (NR 3.8–6.2). Technetium thyroid scan showed markedly suppressed uptake function throughout both lobes consistent with thyroiditis.

No defects were detected on formal visual field testing. Chest radiography and serum angiotensin converting enzyme (ACE) concentration were normal. Serological investigations for HIV and syphilis were negative.

Antinuclear antibodies were weakly positive (1:40, diffuse pattern). Thyroid microsomal, thyroglobulin, adrenal, parietal cell, smooth muscle, mitochondrial antibodies, and thyroid stimulating immunoglobulins were all negative.

Head computed tomography (CT) scanning was normal; however, the pituitary was not specifically examined.

Magnetic resonance imaging (MRI) [Figures 1,2] showed enlarged pituitary gland (15mm × 12 mm × 12 mm) with a convex upper border extending up to the under-surface of the optic chiasm displacing the hypothalamus and the neurohypophysis. The enhancement was homogeneous with no specific evidence of a dynamic sequence to suggest a microadenoma. There was loss of the normal high signal within the posterior pituitary. The pituitary stalk was noted to be thickened and strongly enhancing. The brain was otherwise normal with no specific evidence of encephalitis or other infectious process.

With strong suspicion for lymphocytic hypophysitis he was managed nonoperatively and commenced on cortisol replacement therapy with marked symptomatic improvement. He was discharged on a maintenance dose of steroids and is currently on regular endocrine follow-up.
At 3 months follow-up, the patient remained well, though still requiring hydrocortisone. On endocrine testing, he became hypothyroid (TSH <0.1mU/L, FT4 4 pmol/L, FT3 1.9 pmol/L) and remained hypogonadal, requiring thyroid and testosterone replacement therapy. Reimaging of the pituitary at that time (Figure 3) showed reduced size though it remained somewhat enlarged. There was still slight prominence of the upper part of the pituitary stalk, but less marked than on the initial scan.
Lymphocytic hypophysitis is a rare inflammatory condition characterised by marked lymphocytic infiltration, fibrosis, and ultimate destruction of the anterior pituitary gland. Depending on the stage of the disease, the pituitary gland may be either enlarged by inflammation or shrunken by atrophy and fibrosis.\textsuperscript{1}

Knowledge of this condition is largely anecdotal; the cause, incidence, and natural history are unknown. Cases are usually discovered at biopsy and at surgical intervention for a presumptive pituitary neoplasm.

The disease has a strong female predilection of approximately 8.5:1; it commonly affects young women during late pregnancy or in the postpartum period.\textsuperscript{2}

Nearly 379 cases have been reported since the first description of the entity in 1962 from an autopsy conducted on a 22-year-old woman who was 14 months postpartum. She developed shock and died from adrenocortical insufficiency 8 hours following an appendectomy.\textsuperscript{3,4}

Due to greater awareness, better diagnostic neuroimaging, and surgical techniques (such as microsurgical transphenoidal exploration of the sella), lymphocytic hypophysitis is now diagnosed with increasing frequency, and there is an apparent change in its presentation. The disease is now known to occur in both sexes and at all ages. About 15\% of reported cases occurred in men.\textsuperscript{2,5,6}

Most patients manifest varying degrees of hypopituitarism, hyperprolactinaemia, or both. Although the principal site of involvement was considered to be the adenohypophysis, a small number of patients had clinical evidence of diabetes insipidus.\textsuperscript{6,7}

Lymphocytic hypophysitis may present with several clinical forms such as adenohypophysitis (LAH), more commonly affecting young women; infundibuloneurohypophysitis (LINH), affecting both sexes equally; or both (panhypophysitis, LPH), slightly more common in women.\textsuperscript{8}

The cause of lymphocytic hypophysitis remains poorly characterised. However, the greater incidence of the disease in females; its occurrence in close temporal proximity
to pregnancy in most of the cases reported; the presence of associated autoimmune endocrinopathies; and the presence of lymphocytic infiltration have led to the speculation that lymphocytic hypophysitis is an autoimmune disease. As many as 30% of patients with lymphocytic hypophysitis may also have associated autoimmune diseases including thyroiditis, adrenalitis, pernicious anaemia, and parathyroiditis.

Specific serum markers are not currently available and are subject of research at leading centres around the World. Pituitary autoantibodies have been detected in up to 70% of biopsy-proven cases. Further studies may ascertain the importance of secretogranin II autoantibodies as markers for lymphocytic hypophysitis.

Lymphocytic hypophysitis should be considered in the differential diagnosis of pituitary masses (or sellar lesions) in females during pregnancy or in the postpartum period. In addition, those patients (both men and women) in whom pituitary hormone deficiency is noted in association with a coexisting autoimmune disorder are also affected.

Early diagnosis is important because the concomitant pituitary insufficiency is often rapidly progressive and prompt hormonal replacement, especially for hypoadrenalism, is essential.

Hypofunction of the anterior pituitary is more severe and seems to develop earlier in lymphocytic hypophysitis than in pituitary adenomas. It more often concerns corticotrophic and thyrotrrophic functions (56% and 40%) than in pituitary adenoma, in which the somatotrophic and gonadotrophic functions are usually the first to be impaired.

The association with other autoimmunological conditions, usually a thyroiditis, may be a diagnostic hint for lymphocytic hypophysitis. The CSF findings of lymphomonocytic pleocytosis with the negative viral cultures and the absence of clinical meningitis, is likely to be an aseptic meningeal reaction to pituitary inflammation.

MRI findings suggestive of an inflammatory pituitary process include:

- Symmetric enlargement of the pituitary gland.
- Triangular shaped pituitary gland and/or affecting the diaphragma sellae, with homogeneous enhancement.
- Suprasellar extension, especially “tongue-like” extension.
- Diffuse thickening of the pituitary stalk with or without enhancement after gadolinium and loss of the normal posterior ‘bright spot’ on T1-weighted images, where neurohypophysis is involved.

Although no single feature above is pathognomonic of lymphocytic hypophysitis, their simultaneous presence will confer a higher amount of diagnostic reliability. However, the diagnosis can only be clearly established by histologic examination.

Management of lymphocytic hypophysitis is controversial as the natural history is not known. Progressive and permanent hypopituitarism or spontaneous recovery have been reported.

If the diagnosis is strongly suspected, medical treatment alone has been advocated because of the transient endocrine and compressive features of this condition in many instances.

Whereas surgery for mass effect in lymphocytic hypophysitis invariably led to rapid relief of neurological symptoms, endocrinological improvement was seldom
reported. In some patients, however, surgery led to further deterioration in pituitary gland functions or was followed by recurrence of symptoms. If symptoms do not improve with conservative management, transphenoidal surgery for diagnosis confirmation and decompression is advised. To avoid extensive unnecessary surgery, a preoperative frozen section cytology should be performed to confirm the diagnosis. A pituitary experienced neurosurgeon would remove abnormal tissue and preserve normal-looking tissue to minimise the risk of hypopituitarism. Immediate surgery is indicated when there are signs of optic nerve compression or increased intracranial pressure.

Several authors have suggested a therapeutic trial with supraphysiological doses of glucocorticoids, to decrease the pituitary size and possibly to alter the autoimmune response. Results of these trials have been promising. In other reports, the effect of corticosteroid therapy has been poor or transient and symptoms often returned after cessation of therapy. More recently, other immunosuppressive drugs such as azathioprine and methotrexate have been used in specific cases with poor response to corticosteroids. Stereotactic radiotherapy has been used with success at controlling mass effect symptoms in two patients with lymphocytic hypophysitis and severely affected pituitary function, but more experience with this therapeutic modality is necessary. Although rare, lymphocytic hypophysitis has very important diagnostic and therapeutic implications, considering that it is usually mistaken for tumours that may often require surgical management.

In conclusion, the clinical presentation, occurrence of other autoimmune conditions, CSF examination, endocrine profile, and MRI features can (in many cases) justify an expectant approach without surgical intervention—with or without glucocorticoid therapy and/or other immunosuppressant therapies.

**Author information:** Elham Reda, Specialist Physician; Waikato Hospital, Hamilton

**Correspondence:** Dr Elham Reda, Diabetes Clinic, Waikato Hospital, PO Box 3200, Hamilton. Fax: (07) 839 8811; email redae@waikatodhb.govt.nz

**References:**


