Lymphocytic Hypophysis

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A patient with a chronic lymphocytic hypophysitis (LYHY) following an idiopathic lymphocytic meningitis is described. Computed tomography scan of the sella turcica suggested a pituitary adenoma with suprasellar extension, whereas hormonal investigations showed a functional lesion at the supraptuitary level. A transsphenoidal biopsy revealed diffuse lymphocytic infiltration of the adenohypophysis without characteristics of a sarcoïd lesion. The possible relationship between idiopathic (viral?) lymphocytic meningitis and LYHY is discussed.

KEY WORDS: Lymphocytic hypophysitis; Pituitary pseudotumor

Lymphocytic hypophysitis (LYHY) is a rare syndrome consisting of the diffuse, nongranulomatos lymphocytic infiltration of the adenohypophysis causing pituitary insufficiency in variable combinations [1,3,5,7,9, 10,13–18]. Thus far, LYHY has only been described in women, particularly during pregnancy and the puerperium. The pathogenesis is obscure but possibly autoimmune, in view of the pituitary lymphocytic infiltration, the simultaneous lymphocytic infiltrate of other endocrine organs [10,13,18], and the presence of antipituitary antibodies in a patient with hypophysial insufficiency [15].

Computed tomography (CT) scans of the sellar region have shown that LYHY presents as a well-defined enhancing lesion in the sella turcica with possible suprasellar extension [1,3,16,17] and thus may be confused with a hypophyseal adenoma.

Case Report

A previously healthy 49-year-old woman presented in March 1982 with increasing headache, photophobia, and vomiting. Her history was unremarkable, with neither pregnancies nor abortions. She became menopausal in March 1981.

On admission, general and neurological examinations were normal, except for equivocal neck stiffness. Enhanced CT scan of the brain and the sellar region was normal. Cerebrospinal fluid (CSF) examination yielded 79 cells, mainly lymphocytes, a normal glucose level of 3.4 mmol/liter (CSF serum glucose index 0.6), and a slightly elevated protein level of 0.65 g/liter. Laboratory studies of blood and urine were unremarkable, including a normal serum thyroxine level of 90 nmol/liter. Radiograms of the skull and the thorax were normal. A tentative diagnosis of viral meningitis was made as searches for pathogenic microorganisms such as tuberculosis, syphilis, fungi, and other viruses remained unsuccessful. Within a few weeks all symptoms subsided.

Four months later, the patient was readmitted with excessive fatigue, weakness, cold intolerance, diffuse joint pain, and myalgia. She had no neurological signs and CSF analysis showed minimal lymphocytosis of 13 cells. Serum thyroxine was 43 nmol/liter (normal 70–150 nmol/liter), serum triiodothyronine (T3) 0.7 nmol/liter (normal 1.2–2.8 nmol/liter), and thyroid-stimulating hormone (TSH) < 2 μU/liter (normal 0.1–5 μU/liter). Plasma cortisol was 10.10 μmol/liter at 8 AM (normal 0.25–0.66 μmol/liter) and 0.083 μmol/liter at 4 PM (normal 0.080–0.44 μmol/liter). Serum prolactin (PRL) was mildly elevated at 95 μg/liter (normal 5–20 μg/liter). There were normal TSH and PRL responses to thyrotropin-releasing hormone (TRH). An insulin tolerance test and the ACTH-stimulation test were not performed.

The combination of hypothyroidism without increased TSH, slight adrenal insufficiency, and a normal rise in PRL and TSH to a TRH stimulation test was interpreted as indicating a disturbance at the supraptuitary level (pituitary stalk or hypothalamus). CT scan of the sella turcica revealed a substantial intrasellar enhancing lesion with suprasellar extension (Figure 1A–C). Goldmann perimetry disclosed intact visual fields and
visual evoked potentials were normal on both sides. The presence of a hypophyseal tumor extending to the pituitary stalk with residual functioning of pituitary tissue was not excluded, but a suprasellar lesion with secondary intrasellar extension was thought to be more probable, in view of the normal sella on plain radiography and the results of hormonal tests.

Appropriate laboratory examinations failed to show evidence of malignancy, systemic disease, or specific infection. A transsphenoidal hypophyseal biopsy was deferred and therapy consisted of supplementation with thyroxine and cortisone acetate. Four months later the patient developed mild diabetes insipidus and galactorrhea. Antidiuretic hormone concentration in 24-hour urine sample was decreased at 10 ng/liter (normal 25–250 ng/liter). The PRL level was 80 μg/liter. Diabetes insipidus waned without therapy whereas the galactorrhea disappeared with bromocriptine, 5 mg t.d.s. Two months later the serum PRL level was normal but a control CT scan showed an unmodified sellar lesion. Control plain
radiography of the sella remained normal and angiograms of both carotid arteries showed no elevation of the anterior cerebral arteries. A prolactinoma with suprasellar extension seemed unlikely and the hyperprolactinemia was thought to be caused by pituitary stalk involvement and inadequate amounts of PRL-inhibiting factor reaching the adenohypophysis. Bromocriptine therapy was stopped without recurrence of galactorrhea. Eleven months after the first signs of hypopituitarism, retesting of hormonal functions gave similar results, including a slightly elevated PRL level at 61 μg/liter. The follicle-stimulating hormone (FSH) was normal and the luteinizing hormone (LH) was slightly decreased but there was a normal FSH and LH response on gonadotropin-releasing hormone infusion. Antithyroid, antiparathyroid, and antimitochrondial antibodies were not detected.

A transsphenoidal hypophyseal biopsy was eventually performed 1 year after the first signs of pituitary insufficiency. Microscopic examination showed fragments of adenohypophyseal tissue infiltrated by numerous lymphocytes (Figure 2). Epitheloid histiocytes and giant cells were absent. Islands of pituitary cells or isolated pituitary cells were seen scattered between lymphocytic infiltration. These cells were acidophilic as well as basophilic and chromophobic. Immunostaining showed the presence of immunoreactive PRL, growth hormone, adrenocorticotrophic hormone, TSH, FSH, and luteotrophic hormone. A few small fragments consisted of fibrous tissue with numerous cholesterol clefts surrounded by sporadic foreign body type giant cells and dense infiltration with lymphocytes and plasma cells. A small area of old hemorrhage with iron pigment granules and siderophages was seen. Stains for microorganisms were negative. As there were no histological findings compatible with sarcoidosis or with nonspecific granulomatous hypophysitis, LYHY seemed the most likely diagnosis. The postoperative period was uneventful and the patient remained well with hormonal supplements; the headache did not recur. Control CT scans 6 months and 2½ years later showed no recurrence of the sellar lesion.

Discussion
The association of pituitary insufficiency with a well-defined substantial sellar lesion on CT scan suggested a hypophysial adenoma, though this was unlikely with a normal skull x-ray [5]. Furthermore, adequate responsiveness to pituitary stimulation tests and the occurrence of a transitory vasopressin deficiency appeared to conform with a disconnection of the hypophysis and the hypothalamus [5,20]. A functional lesion of the pituitary stalk seemed probable, as no pathology of the hypothalamus could be demonstrated on CT scan. The nature of the lesion was thought to be either neoplastic or inflammatory in origin. Appropriate laboratory investigations failed to demonstrate a primary malignancy, and in view of the minimal progression a metastatic lesion seemed unlikely [23]. Specific infections were not present. Systemic diseases were considered, especially a suprasellar sarcoid granuloma in view of its frequent combination of adenohypophyseal insufficiency and diabetes insipidus [21]. Appropriate examinations for the
detection of systemic sarcoidosis including radiograms of the thorax, a muscle biopsy, and determination of the serum angiotensin converting enzyme showed no abnormalities. These did not exclude a neurosarcoid lesion but made it quite improbable. A giant cell granuloma of the pituitary gland was also possible: in these cases an aspecific chronic inflammatory lesion involves the hypophysis and may have a chronic fluctuating course [12,22]. The presence of either a sarcoid lesion or a giant cell granuloma was considered to be the most probable, but microscopic examination provided evidence of an unexpected LYHY.

Lymphocytic hypophysitis is a very rare syndrome usually presenting with panhypopituitarism; some cases presented with a life-threatening adrenal insufficiency, but milder forms have been described [1,16,17]. Microscopic examination displays pituitary infiltrates composed of lymphocytes and plasma cells, lymphoid follicles, and interstitial fibrosis. The absence of nodular aggregates of epithelioid histiocytes and multinucleated giant cells differentiates LYHY from sarcoid granuloma and nonspecific hypophysitis granuloma.

As all previous patients were women and a majority of cases occurred during pregnancy or soon after childbirth LYHY has been considered as a distinct disease of pregnancy [3]. Some arguments support the view that an autoimmune mechanism could be implicated. In patients with LYHY other endocrine organs have been found to be simultaneously infiltrated with lymphocytes [10,13,18]; autoantibodies to other endocrine organs, and in one case against pituitary cells, have been detected [15]. In cases of polyglandular failure of autoimmune origin, the presence of an autoimmune hypophysitis has been hypothesized [2]. Bottazzo et al [4] identified autoantibodies to PRL-secreting cells in about 7% of patients having one or more autoimmune endocrine diseases. On the other hand, Engelberth and Ježkova [8] found these autoantibodies in 18% of women during the first week after childbirth and Shanklin [19] demonstrated at autopsy that 43% of apparently normal pituitaries were infiltrated with lymphocytes. Pituitary lymphocytic infiltration and the finding of antipituitary antibodies thus represent a frequent and aspecific finding and the relation to LYHY remains unclear.

Another possible contributing pathogenic factor emerged from the present case. A few months earlier our patient displayed severe headache due to lymphocytic meningitis. Review of the histories of 14 cases with LYHY revealed that in four [1,15–17] pituitary insufficiency was preceded by severe and persisting headache, but results of CSF analysis in these cases are absent. As severe headache is not a feature of pituitary insufficiency, we suggest that in some cases lymphocytic meningitis may have been present. The relationship between idiopathic (viral?) lymphocytic meningitis and LYHY is uncertain. It is possible that a virus may induce an antipituitary autoimmunity by inducing the formation of monoclonal antibodies to endocrine organs, including the hypophysis [2]. This mechanism is still speculative but it has been described in animals [11].

In conclusion, when a patient presents with pituitary insufficiency and a sellar/suprasellar enhancing lesion is visible on CT scan, LYHY must be included in the differential diagnostic considerations, especially when the findings on the CT scan contrast with normal radiography of the sella. Our case further illustrates that LYHY may have a nonprogressive chronic course and that the functional lesion may be situated at the pituitary stalk level. The possibility of a preceding or concomitant lymphocytic meningitis as a possible etiological factor deserves further consideration, especially when an episode of severe and unexplained headache preceded or accompanied LYHY.

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