Lymphocytic Hypophysitis with Involvement of the Cavernous Sinus and Hypothalamus

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Two cases of lymphocytic hypophysitis are reported, in which hypothalamic involvement causing diabetes insipidus was a prominent clinical feature. In one case, a man had clinical and radiological evidence of the involvement of the cavernous sinus. This represents the second reported case of a man with lymphocytic hypophysitis. A transsphenoidal biopy established the diagnosis in both cases. Neither the involvement of the cavernous sinus nor permanent diabetes insipidus has been reported previously. A review of the literature is provided. (Neurosurgery 28:440–444, 1991)

Key words: Hypopituitarism, Lymphocytic hypophysitis. Pituitary mass lesion, Transsphenoidal surgery

INTRODUCTION

Lymphocytic hypophysitis is a rarely occurring inflammatory process of the pituitary gland, first reported by Goudie and Pinkerton (7) in 1962. All reported cases except one have been in women (8, 13). Most patients have become symptomatic during or within 1 year of pregnancy (2–5, 7, 12, 19). Amenorrhea after delivery is the most common initial symptom noted clinically (18). The radiologic and endocrine findings are similar to those for a nonsecretory pituitary adenoma, or other sellar mass lesion, requiring a biopsy for definitive diagnosis. Transient diabetes insipidus has been reported in only one patient (20), whereas the involvement of the cavernous sinus has not been demonstrated.

We report two cases of lymphocytic hypophysitis that resulted in chronic diabetes insipidus, one in a man who also had variable extracranial muscle palsies. Angiography and magnetic resonance imaging (MRI) confirmed the involvement of the cavernous sinus in his case.

CASE REPORTS

Case 1

A 40-year-old man was referred for evaluation of a possible pituitary tumor. His complaints consisted of malaise, bifrontal headaches, weight gain, impotence, polyuria, and polydipsia for 3 months. Six days before admission he experienced an increase in his headaches with persistent vomiting and horizontal diplopia. His past medical history was remarkable for a mother and sister with diabetes mellitus.

The physical examination revealed an obese, slightly lethargic man who did not appear to be cushingoid. The temperature was 36.4°C, blood pressure was 110/70 mm Hg, and pulse was 80. There was no papilledema, and his neck was supple. His abdomen was without striae. On the neurological examination, he was fully oriented. The oculomotor examination showed bilateral palsies of the 6th nerve with equal reactive pupils. Visual fields and activities were within the normal range. The remainder of the neurological examination was within normal limits.

A computed tomographic (CT) study with contrast enhancement revealed a mildly enlarged pituitary gland with homogeneous enhancement and some thickening of the pituitary stalk (Fig. 1). There was no significant suprasellar involvement. A chest x-ray showed no abnormalities. The specific gravity of the urine was 1.005, and the serum electrolyte levels were within normal limits. The afternoon cortisol level was less than 1 μg/dl (normal, 3–12 μg/dl), with a normal response to cosyntropin stimulation. The prolactin level was 13.6 ng/ml (normal, 0–12 ng/ml). Thyroid hormone, thyroid-stimulating hormone, luteinizing hormone, follicle-stimulating hormone, and growth hormone levels were within normal limits. The testosterone level was 46 ng/dl (normal, 270–1200 ng/dl). The patient was started on dexamethasone, and his headache lessened.

A lumbar puncture revealed an opening pressure of 160 mm H₂O, a total protein level of 34 mg/dl, and a glucose level of 82 mg/dl. The cerebrospinal fluid contained 10 nucleated cells, 73% of which were lymphocytes. Diabetes insipidus was confirmed by a water deprivation test. The patient kept his serum sodium well regulated with oral free water intake.

MRI and angiography. MRI revealed a sellar mass, meas-
tissue surrounding the left carotid artery, suggesting infiltration of the cavernous sinus (Fig. 2).

Carotid angiography showed no abnormalities on the right side. The carotid siphon on the left side was open, without lateral displacement, suggesting the involvement of the cavernous sinus (Fig. 3).

Operation. Surgery was delayed because of a small pulmonary embolus from a deep venous thrombus of the left leg. Dexamethasone was discontinued when the patient developed bacteremia caused by Staphylococcus aureus. At that point, the 6th nerve palsies were less severe. The erythrocyte sedimentation rate (ESR) was 131 mm/h (normal, 0–25 mm/h) when the patient was not on steroids.

Approximately 1 month after admission, the patient awoke with a complete 3rd nerve palsy of the left side and decreased sensation in the distribution of the 1st and 2nd divisions of the left trigeminal nerve. Emergent CT and MRI studies were unchanged from those performed on admission.

A transphenoidal approach was used to remove the patient’s sellar lesion. The floor of the sella was markedly thinned. The sella was filled with an avascular, gray fibrous tissue that was poorly demarcated from the pituitary tissue in the posterosuperior aspect of the sella. Most of the abnormal tissue was removed.

Pathological features. The tissue obtained consisted predominantly of adenohypophysal cells with an extensive, chronic inflammatory infiltrate composed of lymphocytes, plasma cells, and histiocytes (Fig. 4). Secretory cell destruction and fibrosis were associated with the inflammatory process. A few small islands of normal secretory cells remained (Fig. 5). A similar process involved the neurohypophysis. No giant cells, granulomas, or germinal centers were found. Special stains were negative for bacterial, fungal, and acid-fast organisms. No evidence of histiocyte X was found. All bacterial cultures were sterile.

Postoperative course: The patient’s headache, left 3rd nerve palsy, and bilateral 6th nerve palsies resolved before discharge.
Steroids were administered only perioperatively. Diabetes insipidus persisted, and the patient used DDAVP intermittently to regulate his urine output. The patient was discharged on the 5th postoperative day. One month after surgery, the patient's headache, nausea, vomiting, and bilateral 6th nerve palsies recurred. Corticosteroids were resumed, and his symptoms improved. Attempts to taper the steroids were unsuccessful. The patient remained impotent; the testosterone level was less than 10 ng/ml. Testosterone injections were started 3 months postoperatively, and the patient became potent 3 months later.

A CT scan 7 months after surgery showed the pituitary gland to be markedly decreased in size compared with the preoperative studies (Fig. 6). An exacerbation of diplopia responded to an increase in the steroid dose. Ten months after surgery, the patient complained of bilateral hip pain. MRI revealed avascular necrosis of both femoral heads. The steroid dose was tapered; however it was not possible to discontinue corticosteroids until 19 months postoperatively. One month later, the patient underwent a left total hip replacement, requiring only peroperative corticosteroids. The preoperative ESR was 29 mm/h. A right total hip replacement was tolerated without corticosteroid supplementation 2 years postoperatively. Diabetes insipidus persists, thyroid and adrenal functions are within normal limits, and the patient continues to require testosterone injections.

Case 2

A 34-year-old woman, gravida 1 para 0, with regular menses developed headache, thirst, and polyuria, with a 3-gallon per day fluid intake. Over the next 5 months, oligomenorrhea
and then amenorrhea developed, without galactorrhea. Physical and neurological examinations were within normal limits. The specific gravity of the urine was 1.003, and the serum prolactin level was 43 ng/ml; thyroxine, thyroid-stimulating hormone, luteinizing hormone, follicle-stimulating hormone, cortisol, and estradiol levels were within normal limits. Bromocriptine, 7.5 mg/day, resulted in the restoration of menses and lowering of the prolactin level to less than 2.1 ng/ml within 2 months. Thirst and urine volume responded well to DDAVP administration at night. MRI showed diffuse pituitary enlargement, infundibulular thickening, and upward extension of the mass into the suprasellar cistern, both before and after several months of bromocriptine therapy.

Operation. Transsphenoidal surgery revealed a grayish multilobular mass behind the anteriorly situated normal pituitary gland. Except for a small portion that was densely adherent to the dorum sellae and posterior part of the diaphragm, the entire mass was removed.

Pathological features. The lesion consisted of a mixed inflammatory cell infiltrate, which included plasma cells, mature small lymphocytes, histiocytes, and occasional eosinophils, as well as some fibroblasts and collagen. There were no giant cells or granulomas. Immunocytochemical stains revealed that the inflammatory cells included B and T lymphocytes, with both kappa and lambda surface light chains, consistent with a reactive, heterogeneous inflammatory process. Special stains for organisms were all negative, and there was no evidence for sarcoidosis or histiocytosis.

Postoperative course. The patient did well; a year after surgery, she had normal menses, a prolactin level of 6.5, and was taking no drugs other than 0.05 ml of DDAVP at bedtime. A follow-up MRI at this time showed no residual mass, and no other abnormalities. Her clinical condition was unchanged 17 months postoperatively.

**DISCUSSION**

To our knowledge, Case 1 is the second reported case of lymphocytic hypophysitis in a man (8). Additionally, there is only one previous report of lymphocytic hypophysitis causing diabetes insipidus, which was transient (20). Both of our patients appear to have permanent diabetes insipidus. There is no previous report of the involvement of the cavernous sinus either clinically or radiologically. One previous case had a unilateral, transient 6th nerve palsy before the onset of endocrine symptoms, possibly secondary to pseudotumor cerebri (15). There has been no report of ocular motor or trigeminal nerve involvement.

The previously reported male case of lymphocytic hypophysitis required chronic thyroid, corticosteroid, and testosterone replacement (8). At this point, our Case 1 is receiving only testosterone replacement as regards anterior pituitary function; diabetes insipidus is managed with DDAVP at bedtime. Case 2 also requires DDAVP but is otherwise hormonally and neurologically intact.

Lymphocytic hypophysitis may be related to an autoimmune process (2, 12, 14-18, 21). Levine (14) produced a pathologically similar process in rats by the injection of pituitary tissue mixed with Freund's adjuvant. The inflammatory response was more severe in postpartum rats. Antipituitary antibodies have been found in two previously reported cases (15, 21). Lymphocytic hypophysitis has also been associated with autoimmune processes in other organs including thyroiditis, adrenalsitis, and pernicious anemia (7, 11, 16).

Most commonly, patients seek treatment during pregnancy or in the postpartum period for hypopituitarism (2, 3-5, 7, 12, 15, 16, 19); however, symptoms may occur after menopause (6, 11, 13, 20). Often, there is only a minimal increase in sellar content that is not in proportion to the extreme pituitary dysfunction (8). In all previously reported cases, there has been no evidence of an adenoma, hemorrhage, sarcoidosis, syphilis, or tuberculosis.

Our cases are pathologically similar to one reported by McKeel (17) in 1984, in that no germinal centers or granulomas were found. McKeel found ultrastructural similarities between lymphocytic hypophysitis and granulomatous hypophysitis (2, 19). This suggests that lymphocytic hypophysitis and granulomatous hypophysitis may be different phases of the same autoimmune process (9, 17). Miyamoto et al. (18) also reported a case that supports this. Clinically, granulomatous hypophysitis has been associated with a prolactinoma and with a ruptured Rathke's cleft cyst (1, 10). In these cases, a foreign body reaction was implicated. There was no underlying cyst or neoplasm found in either of our cases.

In conclusion, lymphocytic hypophysitis usually occurs in women, commonly mimicking a pituitary neoplasm. Our cases include the second reported occurrence in a man, as well as the first reports with clinical and radiologic evidence of cavernous sinus involvement and with permanent diabetes insipidus. A transsphenoidal biopsy was required for diagnosis. Presumably, when lymphocytic/granulomatous hypophysitis is intense or strategically located in the cavernous sinus, infundibulum, or hypothalamus, manifestations such as those seen in our cases may occur. Thus, ocular palsies and diabetes insipidus should be added to the spectrum of clinical manifestations that may accompany this disorder.

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Gonadotroph Adenoma of the Pituitary Mimicking a Prolactinoma

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In a 41-year-old woman with mild hyperprolactinemia and amenorrhea, preoperative hormonal and neuroradiological findings suggested the diagnosis of a macroadenoma. She underwent transphenoidal surgery since the tumor size had not changed in spite of bromocriptine administration for 5 months. Consequently, this case was diagnosed as a female-type gonadotroph adenoma on the basis of its characteristic ultrastructural features including a honeycomb Golgi complex, even though endocrinological and immunohistochemical findings were not those of a typical gonadotroph adenoma. (Neurosurgery 28:444–449, 1991)