The Widening Spectrum of Lymphocytic Hypophysitis

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A case is presented of a nulligravida found to have widespread anterior pituitary insufficiency, hyperprolactinemia, and central Diabetes Insipidus, after presenting with aseptic meningitis. A cystic intra-sellar mass turned out to be pituitary destroyed by lymphocytic hypophysitis (LH).

In reviewing the relevant literature, the present report suggests that:

(a) The appearance of LH need have no relationship to pregnancy.
(b) Prior aseptic meningitis and/or the occurrence of central DI in a patient with an intra-sellar mass may be clues to the diagnosis of LH.
(c) Biopsy proof of LH might allow for resolution without the morbidity of hypophysectomy and the need for hormone replacement.

Introduction

The traditional view of lymphocytic adenohypophysitis (LH) is that it is an auto-immune disorder of the anterior pituitary, usually occurring during pregnancy or the first year post-partum; and that it can mimic a pituitary adenoma with respect to imaging, mass effects, and hormonal anomalies...but Diabetes Insipidus (DI) does not occur, because the posterior pituitary is not involved. However, recent reports have led to an appreciation of the more varied settings in which this disorder may present. Thus, it may occur unrelated to pregnancy, as well as in men. Central DI has been reported with a prevalence as high as 19% in some series of LH. Theoretically, central DI in LH may result from either inflammatory destruction, or compressive injury (mass effect), of the stalk or posterior pituitary; but, the rarity of DI with pituitary adenomas suggests, perhaps, that the former mechanism is more likely. Some describe a pathologically similar, but presumably rarer and distinct, entity, lymphocytic infundibulo-hypophysitis (LIH), to account for central DI. However, since reports of LIH describe imaging and histology similar to LH, and reports of each describe inflammatory involvement and varying endocrine abnormalities associated with both anterior and posterior pituitary in the same patient, it is reasonable to suppose that there is but one disease with varying extents of pituitary involvement in different individuals.

Awareness of the possible presence of LH is particularly important, since if the diagnosis is confirmed histologically, steroid therapy may be helpful, and spontaneous resolution of the hormonal deficiencies may occur without surgical extirpation.

We describe herein a case whose unusual presentation serves to further emphasize the varied circumstances under which the disease may first appear. This suggests that, unless there is imminent visual loss from optic nerve compression, perhaps all pituitary masses suspected of being LH should be biopsied with careful preservation of normal pituitary tissue, with a view to attempting non-surgical treatment.

Case Presentation

The patient was a 32-year-old white female nulligravida who was hospitalized in December 1996 because of acute onset of meningitis, with severe headache.
vomiting, and progressive lethargy. In the previous 6-8 months, she had lost 27 lb. from anorexia, had suffered from bi-temporal headaches, and had developed amenorrhea without response to a progestin challenge. She was also bothered by recent onset of fatigue, cold intolerance, dry skin, polyuria and polydipsia. There was no hyperpigmentation.

Initial laboratory assessment showed a normal WBC, but a mild normocytic anemia with Hct = 34%. BUN, creatinine, electrolytes, albumin, globulin, liver function tests, glucose and urinalysis were all normal, except for mild hypokalemia (3.4 mEq/L). Lumbar puncture yielded CSF containing 1000 cells/cc., with 50% PMN, 25% lymphocytes, 4% eosinophils, and 17% non-WBC. No organisms were seen on Gram stain. CSF protein concentration was 81 mg./dL., and that of glucose, 37 mg./dL. Cultures of both CSF and blood yielded no growth. CSF VDRL, cryptococcal antigen, and latex agglutination to bacterial antigens were all negative. Serum antibodies to Histoplasma, Cryptococcus, Blastomycetes, Coccidioides, Aspergillus, Tularemia and Brucella were all negative. Serum IgG antibody titre to Herpes Simplex was positive, but IgM antibody titre was not. Serum angiotensin converting enzyme (ACE) was 102 U/L (19-79).

Chest x-ray showed no radiologic evidence of Sarcoidosis, and was read as normal.

Imaging studies of the brain (Fig 1.) showed a mixed density lesion of the sella turcica, suggestive of a possible pituitary macro-adenoma with cystic necrosis. There was no associated calcification. The infundibulum was not clearly visualized.

Vomiting abated and she seemed to improve; but shortly thereafter, it recurred with diarrhea, headache and hypotension. A 24-hour urine for free cortisol showed none detectable (<14 mcg). The patient was given parenteral gluco-corticoids and responded nicely.

A prolactin level was modestly elevated at 65.9 ng./mL. T-4 was low at 4.2 mcg./dL. (5-12) and serum T3 was low-normal, at 82 ng./dL. (80-180), but TSH was only 0.84 mcU/mL (0.40-5.50). Serum estradiol was <10 pg./mL. (30-400), with both FSH and LH non-elevated. IGF-I level was low at 104 ng./mL. (114-492). She was found to have central DI, after an overnight water deprivation test led to serum hyper-osmolality (317 mOsm/L.), plasma ADH <1.0 ng./mL. (1.0-13.3), and urine osmolality only 262 mOsm/L.

Formal perimetry disclosed no evidence of visual field defect in the right eye, and a possible superior constriction in the left.

Thus, generalized anterior pituitary insufficiency and central DI were clearly established. To explain both the relatively low level of prolactin as well as the aseptic meningitis, it was posited that she had an expanding non-secretory macro-adenoma resulting in anterior hypopituitarism, central DI and dopaminergic inhibition from stalk compression, and auto-infarction with meningeal penetration.
After appropriate replacement with glucocorticoids, L-thyroxine, and DDAVP, she underwent trans-sphenoidal surgery. Upon entry to the sella, a fibrotically encapsulated cyst was encountered which, upon puncturing, exuded thick, tan fluid. No definite pituitary gland was visualized, although the infundibulum was recognized. Smears of the fluid revealed mucous debris and rare PMN’s. Sections of the capsule showed most of the normal pituitary parenchyma replaced by fibrous tissue, mature lymphocytes, a few plasma cells, and aggregates of foamy macrophages (Fig 2). No granulomata, giant cells, or neoplasm were noted, and special stains were negative for AFB and fungi.

She has recovered from surgery, and is currently on intra-nasal DDAVP, 10 mcgm. bid, L-thyroxine, 0.1 mgm./d., prednisone, 4 mgm. po q AM and 2 mgm. q AM, conjugated equine estrogen, 0.625 mgm./d., and hydroxyprogesterone acetate, 2.5 mgm./d. She has good energy and appetite, and no nocturia. Electrolytes, BUN, creatinine, free T4, and serum T3 are all normal. Serum TSH is non-detectable (<0.03 mcU/mL). Serum prolactin level and CBC have both returned to normal. No attempt has been made to withdraw her from replacement hormones. On one occasion, when she forgot her morning dose of DDAVP, intense polyuria returned in a few hours.

Discussion

The diagnosis of LH is reasonably well established. Giant cell granuloma of the pituitary could produce similar radiologic and endocrine findings, but the histologic picture is inconsistent with this diagnosis. Further, the absence of osseous involvement, and the lack of eosinophils and Langerhans histocytes rules out Histocytosis X. Finally, although the ACE level was elevated, the lack of granulomata, the normal chest x-ray and the absence of hyperglobulinemia make Sarcoidosis untenable.

The fact that our patient was a nulligravida again emphasizes that LH need not have any relationship to pregnancy; and so, should correspondingly broaden the clinician’s differential diagnosis of the pituitary mass.

Unfortunately, when it was first realized that there was intra-sellar pathology, she already had, except for hyperprolactinemia, symptomatic pan-hypopituitarism, with the gland severely damaged. This recalls the fact that undiagnosed hypopituitarism from LH may be fatal.6

The occurrence of aseptic meningitis with slight elevation of CSF protein, in association with LH, has been described at least twice before. Vanneste and Kamphorst7 reported a case of LH four months after an episode of aseptic meningitis. They raised the question of whether the meningitis, by viral-mediated immuno-logic mechanisms, may have caused LH. But in both the case of Paja et. al7 and in ours, aseptic meningitis was long preceded by signs of hypopituitarism, so it is likely that meningeal involvement reflected CSF invasion by the expanding inflammatory pituitary mass. Regardless of the mechanisms involved, we believe that a history of aseptic meningitis in association with a sellar mass should raise the question of LH.

Also amplified by our case, the presence of central DI, in association with a sellar mass, should suggest LH, since their concurrence has been shown8 to be not uncommon, while DI is rarely seen with pituitary adenomas.

Although elevated, the prolactin level was not at the level typically associated with macro-prolactinomas; and we postulated that the hyperprolactinemia was
due to stalk compression. This was confirmed by the normalization of serum prolactin following surgical decompression. Although we did not use bromocriptine, lowering of prolactin level with failure of the mass to shrink in response to this drug, would suggest that the mass is not a prolactinoma, and so raise the possibility of LH.

The clinical course of LH is highly variable. As stated above, it may be lethal if it causes untreated hypopituitarism. Yet, some cases are associated with spontaneous resolution. Some have reported a beneficial effect of steroid therapy in shrinking the mass and restoring pituitary function in LH; but in other proven cases, such treatment has been ineffective.

In our case, the histologic picture, the post-operative non-detectable TSH level, and the continued need for DDAVP, all suggest permanent hypopituitarism. Yet, despite its inconsistent results, we think that, in the absence of imminent potential catastrophe from mass effects, a trial of anti-inflammatory steroid therapy is merited in those cases suspected early on clinical grounds of being LH; or proven at operation by biopsy, with careful preservation of normal pituitary tissue. Some patients would be thereby saved from the morbidity associated with hypophysectomy and the need for hormonal replacement.

References: