Lymphoid Hypophysitis in a Patient With Hypoglycemic Episodes

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* Destructive inflammatory processes of the anterior pituitary gland are unusual and are rarely recognized either during life or at autopsy. A woman with recurrent episodes of hypoglycemia was found on autopsy to have a destructive lymphoid infiltrate in her adenohypophysis that appeared to result in only partial hypopituitarism. This lesion is thought to be an autoimmune disorder and has been reproduced experimentally. Four other cases have been reported previously in the world literature and are reviewed in this paper. (Arch Pathol Lab Med 102:46-48, 1978).

Extensive mononuclear infiltrates that are accompanied by interstitial fibrosis and destruction of parenchymal tissue occur in organs, such as the thyroid and the adrenal glands, and are thought to represent autoimmune processes. We have recently encountered an identical destructive inflammatory process in the anterior pituitary in an elderly woman with severe hypoglycemia. We report this case of lymphoid hypophysitis and review the four previously reported cases.1

REPORT OF A CASE

A 59-year-old woman was well until December 1974, when she developed the gradual onset of fatigue, weakness, anorexia, nausea, and she lost 9 kg. In addition, her physician had noted a normocytic anemia with a hematocrit value of 30%. She had had a total abdominal hysterectomy in 1971 for menorrhagia secondary to uterine leiomyomata and adenomyosis.

Results of physical examination on admission to the hospital in February 1975 revealed a slender woman with a blood pressure of 110/70. No abnormal physical findings were recorded. An effective thymine ratio was 0.95 (normal, 0.6 to 1.12) and a fasting blood glucose value was 88 mg/100 ml. Extensive investigations failed to reveal the cause of her symptoms and she was discharged.

In April 1975 the patient was readmitted in a semicomatose, somnolent state. Intravenous fluids were administered and her coma rapidly cleared. A fasting blood glucose value was not obtained on admission, and the results of extensive laboratory testing were unremarkable. A repeat effective thymine ratio was 0.92 and plasma cortisol at 11 AM and 8 AM were 24 and 21 mg/100 ml, respectively.

One month later, she was readmitted to the hospital in a confused, semicomatose state with a fasting blood glucose value of 30 mg/100 ml. Repeated fasting and two-hour-postprandial blood glucose levels were normal except for one morning fasting specimen in which the value was 87 mg/100 ml. A determination of serum insulin level that was made when the patient's blood glucose value was normal was 8 units (normal, 4 to 20 units). Angiograms of the pancreas were unremarkable. Her primary complaint during this admission was arthralgia, which affected the lower extremities, but which was unassociated with objective physical findings.

The patient's final admission occurred in mid-December 1975, when she was again admitted in hypoglycemic coma with a blood glucose level of 25 mg/100 ml. There had been continued loss of weight despite frequent oral feedings, but the patient's major problem had been joint pain involving the knees and the hips. She did poorly, and on the fourth hospital day her plasma sodium level was 107 mEq/liter, plasma potassium level was 2.4 mEq/liter, and plasma chloride level was 68 mEq/liter. Despite attempts to correct these imbalances, the plasma sodium level was measured at 112 mEq/liter on the sixth hospital day. The patient developed evidence of pneumonia and congestive heart failure, and she died.

AUTOPSY FINDINGS

On autopsy, the pituitary gland was enlarged and bulged slightly from the sella turcica. Microscopically, the adenohypophysis was involved with a severe inflammatory process that was characterized by the presence of scattered lymphoid follicles and by a diffuse infiltrate of lymphocytes and plasma cells, the latter accounting for approximately 5% to 10% of the total round cell infiltrate. There was extensive interstitial fibrosis, and only scattered, small residual islands of distorted pituitary cells remained (Fig 1 and 2). Approximately 75% of the normal anterior pituitary cells were destroyed by this process. The posterior pituitary was unremarkable.

The combined weight of the adrenal glands was 8.5 gm and the thyroid gland weighed 14 gm. No histological abnormalities were detected in the thyroid or adrenal glands. The breasts were slightly atrophic, but this was not inconsistent with the patient's age. The ovaries were surgically absent, and results of microscopical examination of two parathyroid glands were normal. There were no pathological abnormalities present in sections of the hypothalamus, and the pancreas was unremarkable except for a slight to moderate islet cell hyperplasia. Special stains to demonstrate cell types and granules of the anterior pituitary and pancreas were unrewarding.

The immediate cause of death was a severe fulminating bronchopneumonia.

COMMENT

This characteristic destructive inflammatory process that is confined to the anterior pituitary has been previously described and variously referred to as lymphoid hypophysitis, anterior hypophysitis, and lymphomatous hypophysitis.5,6 In our patient, there was destruction of approximately 75% to 80% of the anterior pituitary that probably resulted in only partial

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hypopituitarism. The fact that plasma cortisol levels and serum thyroxine levels were normal six months prior to death, and that the thyroid and adrenal glands were normal at autopsy indicate that the adenocorticotrophic and thyrotrophic functions of the pituitary gland were normal. Although pituitary function was incompletely investigated during life, we postulate that there was a deficiency in growth hormone and possibly in gonadotrophins and that the deficiency in growth hormone resulted in episodes of hypoglycemia. In patients in whom there is progressive pituitary destruction, clinical manifestations usually begin when there is approximately 75% destruction, and hormonal deficiencies follow a predictable sequence. Growth hormone and gonadotrophins are the first to fail, followed often much later, by deficiencies in corticotrophin and thyroid stimulating hormone. Wilber and Odell have reported repeated attacks of hypoglycemia that occurred in individuals with isolated deficiencies of growth hormone.

Clinical investigations during life and at autopsy provide no good explanation for our patient's severe arthralgias. Note that no other similar inflammatory process or autoimmune disease was recognized.

Review of the literature indicates that there have been four previously recorded cases with an identical pathological process that involved the anterior pituitary. The pertinent findings in these cases are summarized in the accompanying Table.

All of the patients in the reported cases were women, and their ages ranged from 26 to 74 years. Two cases occurred in young women who had had uncomplicated pregnancies within the previous year, and this lead Egloff et al to postulate that this disease may result from pituitary autoantibodies that develop during or immediately following pregnancy. Three of the cases, however, were clearly unrelated to pregnancy, and two patients were postmenopausal.

In four of five cases, death occurred within a year of the onset of symptoms; and in the other case, fatigue, anorexia, and weight loss were present for seven years prior to death.

In general, the patients complained of nonspecific symptoms such as fatigue, loss of weight, anorexia, and lassitude that undoubtedly reflected pituitary insufficiency. Amenorrhea was present in the only two women who were able to menstruate. In several cases, laboratory data confirmed the clinical suspicion of hypothyroidism, but in two instances thyroid function tests were normal. Several patients exhibited signs and symptoms of adrenal insufficiency and died in what appeared to be an adrenal crisis. Two women had recurrent episodes of hypoglycemic coma, presumably related, at least in part, to

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**Fig. 1.—Pituitary gland showing lymphoid follicles, interstitial round cell infiltrate, interstitial fibrosis and focal collections of pituitary cells (hematoxylin-eosin, × 50).**

**Fig. 2.—Pituitary gland with islands of residual pituitary cells, destructive interstitial inflammation and fibrosis, and nodular collections of lymphocytes (hematoxylin-eosin, × 225).**
growth-hormone deficiency.

The common denominator in all these cases was a destructive inflammatory process that was confined to the anterior pituitary and was characterized microscopically by the presence of lymphoid nodules, a diffuse infiltrate of lymphocytes and plasma cells, and interstitial fibrosis. Small groups of pituitary cells were scattered throughout the adenohypophysis, but these cells were remarkably reduced in number. In three of the five cases, the gland was described as atrophic; in two cases, the gland was enlarged, and in both of these instances, the resulting pituitary insufficiency appeared to be partial.

The pathological process is histologically quite different from so-called granulomatous hypophysitis, in which there are true epithelioid granulomata with multinucleated giant cells.1 Lymphoid hypophysitis may be an autoimmune inflammatory disease, and indeed, the microscopical findings are typical of an autoimmune process. Levine has produced an identical lesion in rats by the injection of rat pituitary tissue and an immunological adjuvant.4 In addition, Engelberth and Jezkova have demonstrated pituitary autoantibodies in the fifth to seventh postpartum day in 23 of 128 patients tested.6 Six to 12 months following delivery, 25% of the patients with elevated pituitary antibodies developed signs of decreased adeno-


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