Lymphocytic Infundibuloneurohypophysisitis as a Cause of Central Diabetes Insipidus

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ABSTRACT

Background Central diabetes insipidus may be familial, secondary to hypothalamic or pituitary disorders, or idiopathic. Idiopathic central diabetes insipidus is characterized by selective hypofunction of the hypothalamic-neurohypophysial system, but its cause is unknown.

Methods We studied 17 patients with idiopathic diabetes insipidus, in whom the duration of the disorder ranged from 2 months to 20 years. Only four patients had been treated with vasopressin before the study began. All the patients underwent endocrinologic studies and magnetic resonance imaging (MRI) with a 1.5-T superconducting unit, and two patients had biopsies of the neurohypophysis or the pituitary stalk.

Results Nine of the 17 patients had thickening of the pituitary stalk, enlargement of the neurohypophysis, or both and lacked the hyperintense signal of the normal neurohypophysis. In the remaining eight patients, the pituitary stalk and the neurohypophysis were normal, although the hyperintense signal was absent. The abnormalities of thickening and enlargement were seen on MRI only in the patients who had had diabetes insipidus for less than two years, and the abnormalities disappeared during follow-up, suggesting a self-limited process. In addition to vasopressin deficiency, two patients had mild hyperprolactinemia and nine had impaired secretory responses of growth hormone to insulin-induced hypoglycemia. The two biopsies...
revealed chronic inflammation, with infiltration of lymphocytes (mainly T lymphocytes) and plasma cells.

**Conclusions** Diabetes insipidus can be caused by lymphocytic infundibuloneurohypophysitis, which can be detected by MRI. The natural course of the disorder is self-limited.

Central diabetes insipidus is a chronic disorder characterized by polyuria and polydipsia due to vasopressin deficiency. The disorder may be familial, idiopathic, or secondary. Familial diabetes insipidus is characterized by autosomal dominant inheritance and, at least in some families, mutations of the vasopressin-neurophysin II genes. Secondary diabetes insipidus, the most common form of the disorder, is caused by tumors, infections, trauma, or other processes (such as histiocytosis and vascular lesions) that damage the hypothalamic-neurohypophysial system. Idiopathic diabetes insipidus, which accounts for 10 to 30 percent of cases of central diabetes insipidus, is characterized by selective hypofunction of the hypothalamic-neurohypophysial system. Antibodies against magnocellular neurons of the hypothalamus have been detected in some patients, leading to speculation that it is an autoimmune disorder. Its pathogenesis, however, is unknown.

Magnetic resonance imaging (MRI) has shown that the normal neurohypophysis generates a hyperintense signal on T-weighted images. Although the origin of this hyperintense signal is not known, it is seen on MRI scans from almost all normal subjects and its intensity disappears after the injection of hypertonic saline. The hyperintense signal is generally not seen in patients with idiopathic or secondary diabetes insipidus.

We undertook this study in an attempt to determine the pathogenesis and pathophysiologic processes of idiopathic diabetes insipidus by MRI and endocrinologic testing. We found abnormalities on MRI scans of the pituitary stalk and neurohypophysis in nine patients and performed biopsies in two of them, which demonstrated lymphocytic inflammation. These investigations provide new insight into the pathogenesis of idiopathic diabetes insipidus.

**Case Reports**

We studied all 17 patients (4 men and 13 women, 28 to 73 years old) admitted to our hospital with idiopathic diabetes insipidus from 1986 to 1992 (Table 1). The diagnosis of idiopathic diabetes insipidus was based on normal computed tomographic (CT) scans of the head, the lack of symptoms and signs of hypothalamic damage other than diabetes insipidus, and the results of endocrine tests. The duration of the disorder ranged from 2 months to 20 years. Four of the 17 patients had been treated with vasopressin (an analogue of arginine vasopressin), which was discontinued at least one week before the study. None of the patients had a family history of diabetes insipidus. One patient (Patient 9) had had hyperthyroidism caused by Graves' disease 30 years before the onset of diabetes insipidus and had a small goiter on admission, but no other patient had any history of autoimmune disease. Patients 1, 2, 3, 4, 5, and 9 had had operations for appendicitis or ectopic pregnancy or had undergone cesarean section. Three patients had positive tests for antinuclear antibodies, and two had positive tests for rheumatoid factor. None of the nine patients tested had antithyroglobulin or antithyroid microsomal antibodies. Tests for antipituitary, antineuronal, and antivasopressin antibodies were not
performed. The results of tuberculin skin tests were either positive or borderline in the 15 patients tested. Serum concentrations of angiotensin-converting enzyme were normal in the 12 patients tested. Chest and bone roentgenograms were normal in all 17 patients, except that Patient 2 had mild cardiomegaly due to mitral stenosis and aortic regurgitation and Patient 5 had pleural thickening. All the patients gave informed consent to the tests.

View this table:  **Table 1.** Clinical Characteristics of 17 Patients with Idiopathic Diabetes Insipidus, According to Results of MRI of the Pituitary Stalk or Neurohypophysis.

The patients were divided into two groups. Group 1 consisted of the nine patients who had abnormalities in the pituitary stalk, neurohypophysis, or both on MRI. Group 2 consisted of the eight patients whose MRI scans were normal except for the absence of the normal hyperintense signal. The cases of the two patients in group 1 who had biopsies of the neurohypophysis or the pituitary stalk are described below.

**Patient 1**

Patient 1 was a 47-year-old woman admitted in 1987. Five months earlier, she had experienced a sudden onset of polyuria and polydipsia, and one month earlier her vision had suddenly become blurred. Her menstrual cycles had been regular. Physical examination was normal except for mild papilledema. The results of routine laboratory tests, skull and other bone roentgenograms, and CT scans of the head were normal. A tuberculin skin test was positive. The cerebrospinal fluid obtained by lumbar puncture had a protein concentration of 32 mg per deciliter and 1 cell per cubic millimeter. The cerebrospinal fluid pressure was normal. MRI revealed thickening of the pituitary stalk and a slight enlargement of the neurohypophysis, but no ventricular dilatation (Figure 1). Because the patient was thought to have a tumor or histiocytosis of this region, frontal craniotomy was performed. A small biopsy specimen obtained from the thickened pituitary stalk showed lymphocytic inflammation (Figure 2A); therefore, no further surgery was performed. Postoperatively, the patient was treated with betamethasone for seven days and then with hydrocortisone, which was gradually withdrawn over the following six months. The papilledema disappeared 40 days after surgery and did not reappear after the cessation of hydrocortisone therapy. The patient's diabetes insipidus was treated with vasopressin. She has remained well, but continues to require vasopressin therapy.
Figure 1. Sagittal T<sub>1</sub>-Weighted MRI Scans in Patient 1.

Panel A and Panel B show scans obtained in August 1987, before (Panel A) and after (Panel B) gadolinium enhancement. The pituitary stalk is thickened; gadolinium enhancement is indicated by the longer arrows. The stalk is less thick on enhanced scans from December 1987 (Panel C) and March 1992 (Panel D). The short solid arrow in Panel A indicates the adenohypophysis, and the outlined arrow indicates the neurohypophysis, with no hyperintense signal.

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Figure 2. Biopsy Specimens of the Pituitary Stalk in Patient 1 (Panel A and Panel C) and the Neurohypophysis in Patient 2 (Panel B).

Panel A shows the infiltration of inflammatory cells, mainly lymphocytes and plasma cells, with scattered eosinophils and histiocytes (hematoxylin and eosin, x420). Panel B shows the infiltration of inflammatory cells, mainly lymphocytes and plasma cells, with histiocytes and vascular endothelial cells (hematoxylin and eosin, x420). Panel C shows infiltrating lymphocytes stained with monoclonal antibody UCHL1, which reacts with CD45-RO in T lymphocytes (brown granular material) (x420).

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Patient 2

Patient 2 was a 55-year-old man who had a sudden onset of polyuria and polydipsia two months before admission in 1988. Physical examination was normal, except for a heart murmur due to valvular disease. A test for antinuclear antibody was positive (with a speckled pattern), but other serologic tests were negative. A tuberculin skin test was positive. The cerebrospinal fluid protein concentration was 34 mg per deciliter, and the cell count was 13 lymphocytes per cubic millimeter. A CT scan of the head was normal, but MRI revealed enlargement of the neurohypophysis (Figure 3). Because of the suspicion of an intrasellar tumor,
transsphenoidal surgery was performed. The neurohypophysis was enlarged, but because a biopsy specimen showed chronic inflammation (Figure 2B), no further surgery was performed. The patient was treated with prednisolone for four months and continues to receive vasopressin; he has remained well since that time.

Figure 3. Sagittal T₁-Weighted MRI Scans from Patient 2.

Panel A and Panel B show scans obtained in March 1988 before (Panel A) and after (Panel B) gadolinium enhancement. The neurohypophysis (long arrow in each panel) is enlarged, with no hyperintense signal. Substantial improvement was noted on MRI scans obtained in August 1988 before (Panel C) and after (Panel D) gadolinium enhancement. In Panel A the white arrow indicates the adenohypophysis, and the outlined arrow the pituitary stalk. In Panel C the short arrow indicates muscle tissue inserted during transsphenoidal surgery.

Methods

MRI

A 1.5-T superconducting MRI unit (Sigma, General Electric) was used. MRI scans were obtained with the spin-echo technique. T₁-weighted images were obtained with a repetition time of 400 or 500 msec and an echo time of 20 or 25 msec. T₁-weighted images enhanced with gadolinium-diethylenetriamine pentaacetic acid were obtained immediately after the injection of 0.1 mmol of the contrast agent per kilogram of body weight.

Endocrinologic Studies

All endocrinologic tests were performed after an overnight fast, with the patient at rest. Plasma vasopressin was measured by radioimmunoassay before and after four to eight hours of water deprivation. We measured plasma concentrations of growth hormone, prolactin, luteinizing hormone, follicle-stimulating hormone, thyrotropin, cortisol (all Daiichi Radioisotope Laboratories kits), testosterone (Japan DPC kit), thyroxine (Dainabot Laboratories kit), and thyroxine corticotropin (Mitsubishi Petrochemical kit). Provocative tests were performed on separate days as follows: for thyrotropin and prolactin, a bolus injection of 500 μg of thyrotropin-releasing hormone; for luteinizing hormone and follicle-stimulating hormone, 100 μg of gonadotropin-releasing hormone; for growth hormone, 100 μg of growth hormone-releasing hormone and 0.1 unit of regular insulin per
kilogram of body weight (also for corticotropin and cortisol). Multiple blood samples were collected to measure plasma hormone concentrations before and for up to 120 minutes after the injections.

Histologic Studies

Biopsy specimens were fixed routinely in 10 percent buffered formalin, embedded in paraffin, and stained with hematoxylin and eosin. Immunohistochemical staining with the avidin-biotin complex technique was also carried out in paraffin sections with monoclonal and polyclonal antibodies specific for B or T lymphocytes, Langerhans-cell histiocytosis cells, or endothelial cells. The monoclonal antibodies used were as follows: L26 (Dako) to detect CD20 B cells, antibody MT1 (Bio-Science Products) to detect CD43 T cells, antibody UCHL1 (Dako) to detect CD45-RO T cells, and antibody LN3 (Technicon International) to detect HLA-DR. The polyclonal antibodies used were antibodies against immunoglobulin light chains (Dako), CD3 T cells (Dako), S-100 protein of Langerhans cells (Dako), and factor VIII-related antigen of endothelial cells (Dako).

Results

The clinical characteristics of the 17 patients are shown in Table 1. There were two men in each group. Of the 13 women, all 6 who were premenopausal had regular menstrual cycles. All the women in both groups had had children; all had resumed their menstrual cycles after their pregnancies, and none had had a complicated delivery.

All the patients in group 1 had had diabetes insipidus for less than two years, whereas four of the eight patients in group 2 had had the disease for more than two years. None of the patients had symptoms of anterior pituitary hormone deficiency at the time of admission, and none were taking any medication that might contribute to polyuria, such as a diuretic agent. After Patients 1 and 2, the patients in group 1 were followed without surgery, because the abnormalities on MRI were mild (except in Patient 4) and because, on the basis of our experience in Patients 1 and 2, we expected spontaneous regression of the abnormalities. All the patients received vasopressin therapy. We discontinued this therapy on more than one occasion in all the patients in group 1, but diabetes insipidus immediately reappeared, except in Patient 4. This patient had little polyuria for 10 months, but it then reappeared, and vasopressin therapy was resumed. Eight of the nine patients in group 1 and four of the eight patients in group 2 were followed for more than two years. In none of them did symptoms or signs of hypopituitarism or hypothalamic disturbances other than diabetes insipidus develop.

MRI Scans

The T1-weighted images in all the patients in both groups lacked the hyperintense signal of the neurohypophysis that is seen in almost all normal subjects. The anterior pituitary was normal. As Table 1 and Figure 1 and Figure 3 indicate, seven patients in group 1 had thickening of the pituitary stalk whose intensity was enhanced after the administration of gadolinium. Enlargement of the neurohypophysis was seen in four patients on sagittal images (Figure 3), and its intensity was also enhanced by gadolinium.

The thickening of the pituitary stalk in Patient 1 regressed after surgery and steroid treatment, was a little
greater one year after steroid treatment ended, and had almost disappeared four years after surgery (Figure 1). In Patient 2, the enlargement of the neurohypophysis decreased rapidly after biopsy and steroid treatment (Figure 3). The remaining seven patients in group 1 received only vasopressin therapy. Six had repeated MRI studies more than two years later; in all six the abnormalities on MRI were markedly improved (Table 1), although the hyperintense signal of the neurohypophysis remained absent. The four patients in group 2 who had repeat imaging studies had no changes.

**Endocrinologic Studies**

The results of the endocrinologic studies are shown in Table 2. Urinary osmolality and plasma vasopressin concentrations during water deprivation were low in group 1 despite high plasma osmolality; in only one patient (Patient 8) did urinary osmolality exceed plasma osmolality. In group 2, two patients had slight increases in urinary osmolality and plasma vasopressin concentrations during water deprivation. All the patients had an increase in urinary osmolality in response to exogenous vasopressin (data not shown). Thus, one patient in group 1 and two patients in group 2 could be considered to have partial diabetes insipidus, whereas in the remaining patients it was complete.

**View this table:** Table 2. Results of Endocrinologic Tests in 17 Patients with Idiopathic Diabetes Insipidus, According to Results of MRI of the Pituitary Stalk and Neurohypophysis.

Plasma luteinizing hormone and follicle-stimulating hormone responses to gonadotropin-releasing hormone were normal for age in the men and menstrual status in the women. Plasma testosterone concentrations were within normal limits in all three men tested. All the patients had normal plasma thyroxine concentrations. The plasma thyroid-stimulating hormone responses to thyrotropin-releasing hormone were normal in all 14 patients tested, as were the plasma cortisol responses to insulin-induced hypoglycemia. The basal plasma prolactin concentrations were slightly elevated in 1 patient in each group, and the concentrations increased 160 to 1000 percent in response to thyrotropin-releasing hormone in the 13 patients tested. The plasma growth hormone responses to insulin-induced hypoglycemia were low in one patient, slightly low in five patients, and normal in three patients in group 1 and low in one patient and slightly low in two patients in group 2. The four patients tested with growth hormone-releasing hormone had peak plasma growth hormone concentrations of more than 5 ng per milliliter. These tests were not repeated, because no patient had symptoms or signs of anterior pituitary hormone deficiency during follow-up.

**Histologic Studies**

Microscopical examination of the biopsy specimens from Patients 1 and 2 revealed inflammatory infiltrates composed mainly of lymphocytes and plasma cells, with scattered eosinophils, neutrophils, and histiocytes (Figure 2). Most of the infiltrating lymphocytes stained with MT1, UCHL1 and the antibody against CD3, indicating that they were T cells (Figure 2C). The plasma cells were polyclonal in terms of immunoglobulin light-
chain types. Although some histiocytes were seen, especially in the biopsy specimen from Patient 2, they did not contain S-100 protein. Endothelial cells that stained with antibodies against factor VIII-related antigen and scattered lymphocytes that stained with LN3 were seen in both biopsy specimens. There was no evidence of caseous necrosis or epithelioid granulomas, and no neuronal elements were seen. These findings excluded the possibility of tuberculosis, sarcoidosis, Langerhans-cell histiocytosis, malignant lymphoma, and meningioma.

Discussion

The 17 patients we studied all had clinical features and laboratory findings compatible with idiopathic diabetes insipidus. The diabetes insipidus was complete in 14 patients and partial in 3 patients. The only exceptional finding was transient papilledema in Patient 1, probably caused by inflammation in the pituitary stalk. Some patients, mostly in group 1, had subnormal responses of plasma growth hormone to insulin-induced hypoglycemia, as have been reported in other patients with idiopathic diabetes insipidus. The reason for these subnormal responses is unknown. The plasma growth hormone responses to growth hormone-releasing hormone were normal in all four patients tested, three of whom had slightly low responses to insulin. It appears that there are derangements in the regulation of growth hormone secretion in some patients with idiopathic diabetes insipidus, in either the hypothalamus or the median eminence.

The MRI scans in all 17 patients were compatible with the diagnosis of idiopathic diabetes insipidus, in that the anterior pituitary gland and hypothalamus were normal and the hyperintense signal of the normal neurohypophysis on T₁-weighted images was not seen. Although the hyperintense signal may be present in some patients with idiopathic diabetes insipidus, it is generally absent. In addition, 9 of the 17 patients had thickening of the pituitary stalk, enlargement of the neurohypophysis, or both. The abnormalities were marked in Patients 1, 2, and 4, and we performed biopsies in the first two patients because we suspected a tumor. Histologic examination of the biopsy specimens showed inflammatory infiltrates composed of lymphocytes and plasma cells, with scattered granulocytes. Because the MRI abnormalities regressed in these patients, subsequent patients were simply followed. We cannot be certain that the patients who did not have biopsies had the same abnormalities, but we think it likely, given their MRI results and subsequent courses.

The pituitary stalk may be thickened in patients with Langerhans-cell histiocytosis, which should be carefully differentiated from lymphocytic infundibuloneurohypophysitis. Our patients had no signs of histiocytosis in other tissues and no hypopituitarism, which is often present in this disorder. The histologic findings in the two patients studied differed from those of Langerhans-cell histiocytosis, and staining for S-100 protein, the presence of which is characteristic of histiocytosis, was negative. Primary intracranial plasma-cell granuloma, a rare disorder with plasma-cell and lymphocytic infiltration, can occur anywhere in the brain. If it occurs in the hypothalamus, it can cause diabetes insipidus and hypopituitarism. The histologic findings in our patients were similar to those in patients with plasma-cell granuloma, but no tumor formation was seen, and the clinical course was different. Rare meningiomas contain plasma-cell and lymphocytic components. Our patients had no meningoeipithelial components and no tumor formation. Tuberculosis and sarcoidosis can be ruled out by the absence of granuloma, and the possibility of plasmacytoma can be excluded by the polyclonality of the plasma cells. Lymphoma is also unlikely, because of the lack of atypia and the T-cell phenotype; lymphoma in the
central nervous system is almost exclusively of the B-cell type. Germinoma can also be excluded, given the age and clinical course of the patients.

Only a few previous reports have described patients with lymphocytic inflammation confined to the hypothalamic-neurohypophyseal system. In one patient who had acute onset of diabetes insipidus and subsequently died of bronchopneumonia and another patient who died of an acute attack of bronchial asthma, autopsy revealed lymphocytic inflammation limited to the hypothalamic-neurohypophyseal system. An additional patient with diabetes insipidus had biopsies that showed chronic inflammation in the neurohypophysis. The inflammatory cells in these patients consisted of lymphocytes and plasma cells. A few patients with lymphocytic hypophysitis who also had diabetes insipidus have been reported. In these patients, the anterior pituitary was the principal site of inflammation, and anterior pituitary cells were seen among the plasma cells and lymphocytes. In most patients with lymphocytic hypophysitis the lymphocytes are mostly CD4 cells, and there is unequivocal evidence of hypopituitarism. Amenorrhea is the most common initial symptom, but in some women the disorder first becomes evident during pregnancy. MRI usually reveals a large intrasellar mass, which frequently extends toward the suprasellar region. These findings in patients with lymphocytic hypophysitis are distinct from those in our patients. It is therefore likely that the lymphocytic infundibuloneurohypophysitis we describe here is not a variety of lymphocytic hypophysitis.

The natural course of this disorder is also unique. In the two patients who received glucocorticoid treatment after surgery, the width of the pituitary stalk or the size of the neurohypophysis diminished. The lesions regressed spontaneously in other patients. These results suggest that the inflammatory process was self-limited and regressed spontaneously, perhaps after the destruction of all neurons. This sequence is compatible with the autoimmune hypothesis of idiopathic diabetes insipidus. The preponderance of women among our patients and the presence of T-cell infiltration in the tissue also favor this hypothesis, although few of the patients had other autoimmune diseases. We think it likely that patients in group 2, half of whom had had diabetes insipidus for longer than any of the patients in group 1, had the same disorder but that it had regressed before we studied them. Although we have not confirmed the histologic features in many patients with abnormalities on MRI, we think that lymphocytic infundibuloneurohypophysitis is a common cause of what was previously considered to be idiopathic diabetes insipidus.

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Source Information

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