

CENTRAL DIABETES INSIPIDUS IN CHILDREN AND YOUNG ADULTS

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ABSTRACT

Background Central diabetes insipidus is rare in children and young adults, and up to 50 percent of cases are idiopathic. The clinical presentation and the long-term course of this disorder are largely undefined.

Methods We studied all 79 patients with central diabetes insipidus who were seen at four pediatric endocrinology units between 1970 and 1996. There were 37 male and 42 female patients whose median age at diagnosis was 7.0 years (range, 0.1 to 24.8). All patients underwent magnetic resonance imaging (MRI) and periodic studies of anterior pituitary function. The median duration of follow-up was 7.6 years (range, 1.6 to 26.2).

Results The causes of the central diabetes insipidus were Langerhans'-cell histiocytosis in 12 patients, an intracranial tumor in 18 patients, a skull fracture in 2 patients, and autoimmune polyendocrinopathy in 1 patient; 5 patients had familial disease. The cause was considered to be idiopathic in 41 patients (52 percent). In 74 patients (94 percent) the posterior pituitary was not hyperintense on the first MRI scan obtained, and 29 patients (37 percent) had thickening of the pituitary stalk. Eighteen patients had changes in the thickness of the pituitary stalk over time, ranging from normalization (six patients) or a decrease in thickness (one patient) to further thickening (seven patients) or thickening of a previously normal stalk (four patients). Anterior pituitary hormone deficiencies, primarily growth hormone deficiency, were documented in 48 patients (61 percent) a median of 0.6 year (range, 0.1 to 18.0) after the onset of central diabetes insipidus.

Conclusions Most children and young adults with acquired central diabetes insipidus have abnormal findings on MRI scans of the head, which may change over time, and at least half have anterior pituitary hormone deficiencies during follow-up. (N Engl J Med 2000;343:998-1007.)

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cell histiocytosis^{2,3}; inflammatory, autoimmune, and vascular diseases^{4,5}; trauma resulting from surgery or an accident⁶; and in rare cases, genetic defects in the synthesis of vasopressin that are inherited as autosomal dominant or X-linked recessive traits.⁷⁻⁹ However, 30 to 50 percent of cases are considered idiopathic.¹⁰⁻¹⁵

Arginine vasopressin is transported from the hypothalamus through the neural component of the pituitary stalk and stored in nerve terminals in the posterior pituitary. In many normal subjects, the posterior pituitary is hyperintense on sagittal T₁-weighted magnetic resonance imaging (MRI). The absence of this finding serves as a nonspecific indicator of central diabetes insipidus,^{2-4,16-18} but the frequency of hyperintensity decreases with age in normal subjects.¹⁹ The finding of a thickened infundibulum or pituitary stalk (or both), although not specific, suggests the presence of an infiltrative disease.^{1-5,14,16,17,20} The frequency of these radiologic abnormalities in patients with central diabetes insipidus is poorly defined. We therefore investigated the clinical presentation, the morphologic characteristics of the pituitary region on MRI, and the size of the pituitary stalk over time in patients who had central diabetes insipidus with a variety of causes.

METHODS

Patients

We reviewed the data bases of four pediatric endocrinology units to identify all patients who had documented cases of central diabetes insipidus between 1970 and 1996 and to record family histories, presenting features, hormone concentrations, and the results of imaging and genetic studies at diagnosis and during follow-up. Seventy-nine patients (37 males and 42 females) ranging in age from 0.1 to 24.8 years at diagnosis were seen at these units during this interval, 45 since 1991. The median age at diagnosis was 7.0 years. The clinical protocols used at each center were approved by the appropriate review boards, and written informed consent for all invasive procedures was obtained from the patients or their parents or guardians. The median duration of follow-up through May 1998 was 7.6 years (range, 1.6 to 26.2). All patients had permanent central diabetes insipidus and were being treated with desmopressin acetate (desamino-D-arginine-8-vasopressin), two or

CENTRAL diabetes insipidus is a heterogeneous condition characterized by polyuria and polydipsia due to a deficiency of arginine vasopressin. In many patients, especially children and young adults, it is caused by the destruction or degeneration of the neurons that originate in the supraoptic and paraventricular nuclei of the hypothalamus. Known causes of these lesions include germinoma¹ and craniopharyngioma²; Langerhans'-

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three times daily, either intranasally (in the case of 78 patients) or orally (in the case of 1 patient). Anterior pituitary hormone deficiencies were treated as appropriate.

Diagnosis and Classification of Central Diabetes Insipidus

The diagnosis of central diabetes insipidus was based on a history of polyuria and polydipsia, the results of a physical examination, laboratory evidence of arginine vasopressin deficiency, and imaging studies of the brain and pituitary gland. Cases were further classified on the basis of the probable cause of central diabetes insipidus: Langerhans'-cell histiocytosis (biopsy-proven), an intracranial tumor (including those occurring after tumor resection), familial disease (at least one additional family member had to be affected), skull fracture (i.e., post-traumatic disease), and autoimmune polyendocrinopathy. Cases with no identifiable cause were considered idiopathic.

Posterior Pituitary Function

In 17 patients the diagnosis of central diabetes insipidus was based on the clinical findings of polyuria and polydipsia, an osmolality of less than 300 mOsm per kilogram of water or a specific gravity of less than 1.010 in a 24-hour urine specimen, and an increase in urinary osmolality in response to desmopressin acetate. In 62 patients, a water-deprivation test was performed in which water was withheld for 4 to 14 hours.²¹ A ratio of urinary osmolality to plasma osmolality of 1.0 or less was taken to indicate the presence of complete central diabetes insipidus, and a ratio of more than 1.0 but less than 1.4 was taken to indicate partial central diabetes insipidus. Serum sodium, plasma and urinary osmolality or specific gravity, and plasma immunoreactive arginine vasopressin were measured at the beginning (time 0) and the end of the test. At the latter time, the plasma arginine vasopressin concentrations in normal subjects ranged from 2 to 5 pg per milliliter (1.8 to 4.6 pmol per liter).

Anterior Pituitary Function

Anterior pituitary function was assessed in 64 patients. In 58 of these 64 patients, serum growth hormone was measured before and 30, 60, 90, and 120 minutes after the administration of arginine (0.5 g per kilogram of body weight, given intravenously over a period of 30 minutes), insulin (0.1 U per kilogram, given intravenously), or levodopa (500 mg per square meter of body-surface area, given orally). Patients with serum growth hormone concentrations of less than 10 ng per milliliter and a deceleration in the rate of growth were considered to have growth hormone deficiency. The pituitary-thyroid axis was assessed every 6 to 12 months by measuring serum free thyroxine, free triiodothyronine, and thyrotropin. Hypothyroidism was defined as a low or low-normal serum thyrotropin concentration and low serum free thyroxine and free triiodothyronine concentrations. Plasma corticotropin and serum cortisol were measured in the morning at presentation in 57 patients and every 6 to 12 months thereafter in 41 patients.

Corticotropin deficiency was defined by either a serum cortisol concentration of less than 3.6 μ g per deciliter (100 nmol per liter) in the morning or a peak serum cortisol concentration of less than 20 μ g per deciliter (550 nmol per liter) during insulin-induced hypoglycemia. Serum follicle-stimulating hormone and luteinizing hormone were measured before and 30, 60, and 120 minutes after the intravenous administration of 100 μ g of gonadotropin-releasing hormone per square meter in patients who were thought to have hypogonadotropic hypogonadism. Hypogonadism was diagnosed in boys and girls who had no pubertal development and no increase in serum follicle-stimulating hormone and luteinizing hormone in response to gonadotropin-releasing hormone. Ultrasonography was used to identify female patients with a prepubertal uterus. Serum prolactin was measured in 54 patients at presentation. Standard radioimmunoassays were used to measure all hormones.

Imaging Studies

Computed tomographic (CT) scans were obtained in 22 patients at presentation. MRI scans were obtained in all patients, in 57 of them at presentation. Contrast enhancement (with gadolinium) was used in 65 of the 79 patients. A spin-echo technique with either a 0.5-T system (in the case of 20 patients) or a 1.5-T superconductive system (in the case of 59 patients) was used. Sagittal and coronal T₁-weighted images were obtained in which sections were 3.0 mm thick. In 41 patients, follow-up MRI scans were obtained every 4 to 12 months for a median of 4 years (range, 0.2 to 10.3). On these imaging studies, a normal pituitary stalk was defined as one that was less than 3.0 mm thick.⁶ Thickened stalks were graded as minimally thickened (3.0 to 4.5 mm), moderately thickened (4.6 to 6.5 mm), or severely thickened (more than 6.5 mm). The size of the anterior pituitary was assessed in serial imaging studies in the sagittal plane.

Other Studies

Twenty-three of the patients with idiopathic central diabetes insipidus underwent skeletal surveys to rule out Langerhans'-cell histiocytosis as the cause. Ten patients underwent transfrontal biopsy of the pituitary stalk.

Statistical Analysis

The clinical and laboratory features of the patients were compared with the use of chi-square tests. One-way analysis of variance was used to compare mean values between groups. Odds ratios, with 95 percent confidence intervals, were calculated according to Woolf's method, and the significance of any deviation from unity was estimated with use of Fisher's exact test. We used the Kaplan-Meier method to estimate the probability of a first anterior pituitary hormone deficiency among patients with idiopathic central diabetes insipidus or central diabetes insipidus associated with Langerhans'-cell histiocytosis. Among the patients who had an anterior pituitary hormone deficiency at presentation, we estimated the probability that additional hormonal deficiencies would develop during follow-up. Comparisons between groups were performed with use of the log-rank test. All statistical tests were two-sided. The Statistica 5.1 program (Statsoft, Tulsa, Okla.) was used for all statistical computations.

RESULTS

The characteristics of the 79 patients are reported in Table 1 according to the cause of central diabetes insipidus. Most patients were children when the disease was diagnosed, and the numbers of male and female patients were similar. There was a significant difference ($P < 0.001$) in the age at presentation among the groups (Fig. 1). All five patients with family histories of polyuria and polydipsia were tested, and three had a mutation of the arginine vasopressin-neurophysin II gene.²² In 10 patients, central diabetes insipidus developed during an infectious illness or less than two months afterward (varicella in 5 patients, mumps in 2 patients, and measles, toxoplasmosis, and hepatitis B in 1 patient each). Thirty-two patients had symptoms and signs other than polyuria and polydipsia: headache in 9 patients, a visual defect in 5, growth retardation in 13, fatigue in 4, and failure to thrive in 1. The patient with autoimmune polyendocrinopathy, which was diagnosed during the second year of life, did not have polyuria and polydipsia until the age of 24.8 years.

TABLE 1. CHARACTERISTICS OF 79 CHILDREN AND YOUNG ADULTS WITH CENTRAL DIABETES INSIPIDUS.*

| CAUSE AND FINDINGS | NO. OF PATIENTS (%) | SEX (F/M) | NO. OF PATIENTS WITH SYMPTOMS OTHER THAN POLYURIA AND POLYDIPSIA | AGE (YR) | | NO. OF PATIENTS WITH ENDOCRINE DEFICIENCIES AT LAST VISIT | SIZE OF ANTERIOR PITUITARY ON LAST MRI SCAN |
|----------------------------------------------|---------------------|-----------|------------------------------------------------------------------|------------------|------------------|-------------------------------------------------------------------------------|---------------------------------------------|
| | | | | AT PRESENTATION | AT LAST MRI | | |
| Idiopathic Thickened pituitary stalk | 41 (52) | 23/18 | Growth retardation in 7; headache in 3; fatigue in 3 | 6.4 (0.1–14.9) | 8.0 (0.1–29.9) | GH in 9; GH and TSH in 3; GH and FSH or LH in 3; GH, TSH, and FSH or LH in 2 | Reduced in 17; normal in 1 |
| | 18 (23) | 8/10 | | 7.3 (4.5–11.8) | 7.4 (4.6–11.8) | | |
| Normal pituitary stalk | 19 (24) | 12/7 | Growth retardation in 1; headache in 2; fatigue in 1 | 5.0 (0.5–14.9) | 9.3 (1.1–26.3) | GH in 2 | Normal in 16; reduced in 3 |
| | 4 (5) | 3/1 | | 3.9 (0.1–6.8) | 10.9 (0.1–29.9) | | |
| Langerhans ² -cell histiocytosis† | 12 (15) | 7/5 | Not applicable | 3.4 (1.1–19.6) | 10.0 (1.1–21.3) | GH in 6; GH and TSH in 1; GH and FSH or LH in 1; panhypopituitarism in 1 | Normal in 9; reduced in 3 |
| | | | | | | | |
| Intracranial tumor Germinoma | 18 (23) | 6/12 | Growth retardation in 3; visual defect in 2 | 8.5 (5.8–13.8) | 11.6 (5.8–22.7) | GH and TSH in 1; GH, TSH, and FSH or LH in 2; GH, TSH, and ACTH in 2 | Increased in 4; normal in 2 |
| | 6 (8) | 3/3 | | 10.1 (7.3–13.8) | 10.1 (8.1–13.9) | | |
| Craniopharyngioma | 6 (8) | 2/4 | Visual defect in 3; headache in 3; growth retardation in 2 | 7.5 (5.8–12.0) | 12.8 (5.8–22.7) | Panhypopituitarism in 4; GH, TSH, and ACTH in 1; GH, ACTH, and FSH or LH in 1 | Reduced in 4; could not be evaluated in 2 |
| | 6 (8) | 1/5 | | 9.4 (5.8–17.3) | 9.2 (7.3–20.3) | | |
| Familial | 5 (6) | 5/0 | Failure to thrive in 1; headache in 1 | 1.4 (0.8–7.0) | 4.5 (1.1–35.5) | None | Normal in 4; reduced in 1 |
| Post-traumatic (skull fracture) | 2 (3) | 1/1 | None | 11.9 (10.0–13.8) | 14.8 (13.9–15.7) | Panhypopituitarism in 1; ACTH in 1 | Reduced in 1; normal in 1 |
| Autoimmune polyendocrinopathy | 1 (1) | 0/1 | Not applicable | 24.8 | 24.8 | Not applicable | Normal |

*MRI denotes magnetic resonance imaging, GH growth hormone, TSH thyrotropin, FSH follicle-stimulating hormone, LH luteinizing hormone, CNS central nervous system, and ACTH corticotropin. Values for age are medians and ranges.

†One patient had isolated Langerhans²-cell histiocytosis in the central nervous system.

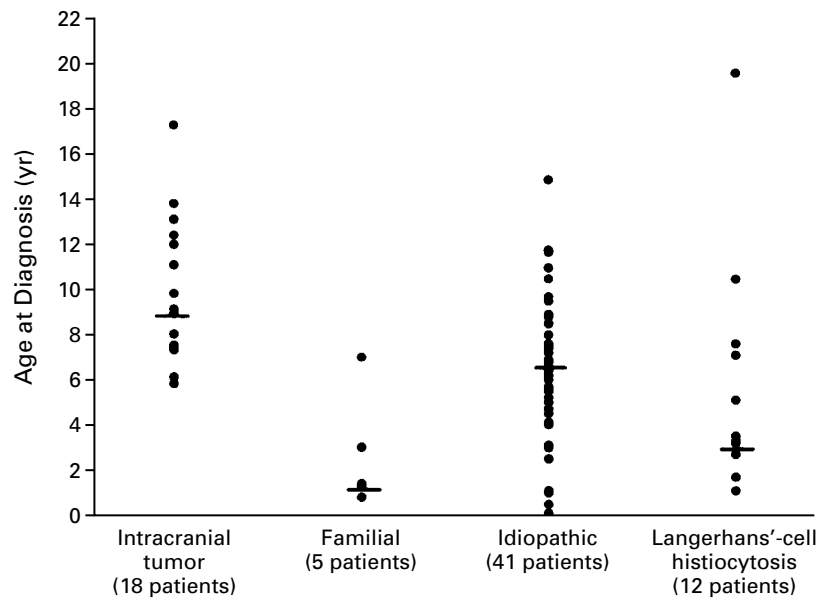


Figure 1. Age at Diagnosis According to the Cause of Central Diabetes Insipidus.

The patients who did not have an intracranial tumor were significantly younger at diagnosis than those who did ($P < 0.001$ for all comparisons). The horizontal lines indicate the medians.

Posterior Pituitary Function

Responses to the water-deprivation test were compatible with the presence of complete central diabetes insipidus in 61 patients and partial central diabetes insipidus in 1 patient. Plasma vasopressin values after the test ranged from 0.5 to 1.5 pg per milliliter (0.5 to 1.4 pmol per liter) in the 21 patients in whom it was evaluated. Urinary osmolality increased to 470 to 780 mOsm per kilogram in response to exogenous desmopressin acetate in the 62 patients tested.

MRI Findings

The posterior pituitary was not hyperintense on the first MRI scan obtained in 74 of 79 patients (94 percent) (Fig. 2). The pituitary stalk was thickened in 29 of the 79 patients (37 percent), 18 of whom had idiopathic diabetes insipidus (Fig. 2C), 5 of whom had Langerhans²-cell histiocytosis (Fig. 3), 5 of whom had a germinoma, and 1 of whom had autoimmune polyendocrinopathy. In 22 patients, the entire pituitary stalk was thickened, whereas in 7 patients, only the proximal portion was thickened. Twelve of 79 patients had MRI findings suggestive of hypothalamic-pituitary tumors: 11 patients had a craniopharyngioma (post-resection in 5) and 1 patient had a post-resection germinoma. The pituitary stalk was normal in 36 patients (46 percent), 19 of whom had idiopathic diabetes insipidus, 7 of whom had Langerhans²-cell histiocytosis, 5 of whom had familial diabetes insipidus, 4 of whom had central nervous system malfor-

mations (the empty-sella syndrome in 2, holoprosencephaly in 1, and cerebral aneurysm in 1), and 1 of whom had a germinoma. The pituitary stalk was transected in the two patients with post-traumatic central diabetes insipidus.

After a median follow-up of 1.5 years (range, 0.2 to 7.5), posterior pituitary hyperintensity was no longer present on the MRI scans of the five patients (6 percent) with hyperintensity on the initial scan, three of whom had idiopathic diabetes insipidus, one of whom had Langerhans²-cell histiocytosis,²³ and one of whom had familial diabetes insipidus. Eighteen patients had changes in their pituitary stalks over time (Table 2). Four patients whose stalk size was normal on the first MRI scan (two with idiopathic diabetes insipidus, one with Langerhans²-cell histiocytosis, and one with a germinoma) had thickening of the stalk after a median of 0.8 year (range, 0.2 to 3.0). Seven patients who had a thickened stalk at presentation (five with idiopathic diabetes insipidus and two with a germinoma) had increases in the thickness of the stalk after a median of 1.6 years (range, 0.8 to 10.3). Six other patients (five with idiopathic diabetes insipidus and one with Langerhans²-cell histiocytosis) with a thickened stalk at presentation had a normal stalk after a median of 1.3 years (range, 1.0 to 5.7) (Fig. 3). One patient with idiopathic diabetes insipidus had a decrease in his initially thick stalk after 2.1 years of follow-up, with no additional changes over a period of 1.4 years. Persistently thickened stalks

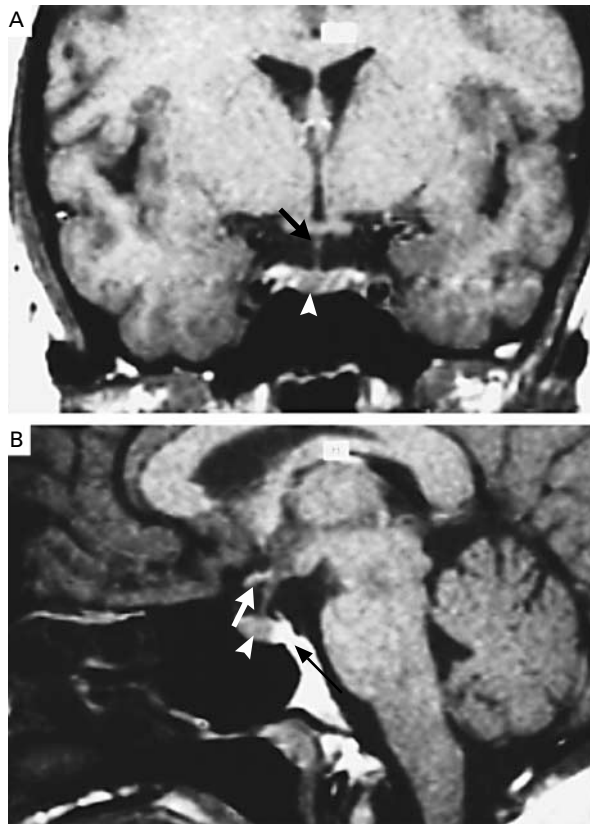


Figure 2. MRI Scans of the Hypothalamic–Pituitary Region in a Normal Subject (Panels A and B) and Two Patients with Central Diabetes Insipidus (Panels C, D, E, and F).

Coronal (Panel A) and sagittal (Panel B) T₁-weighted scans in a normal subject show a normal anterior pituitary (arrowheads) and pituitary stalk (thick arrows) and hyperintensity of the posterior pituitary (thin arrow in Panel B). In a patient with idiopathic diabetes insipidus, coronal T₁-weighted scans with gadolinium enhancement show diffuse cerebral inflammatory disease (black arrows in Panel C) and thickened pituitary stalk (open arrow in Panel C) and spontaneous normalization of brain signals and the size of the pituitary stalk (open arrow in Panel D) during long-term follow-up. Sagittal T₁-weighted scans obtained in a patient with diabetes insipidus caused by Langerhans'-cell histiocytosis show a thickened proximal pituitary stalk (thick arrow), the absence of posterior pituitary hyperintensity (thin arrow), and a smaller-than-normal anterior pituitary (arrowhead) at presentation (Panel E) and a normal-sized pituitary stalk (thick arrow), the absence of posterior pituitary hyperintensity (thin arrow), and a smaller-than-normal anterior pituitary (arrowhead) after three years of follow-up.

were noted in five patients (four with idiopathic diabetes insipidus and one with Langerhans'-cell histiocytosis) over a median follow-up of 4.0 years (range, 3.0 to 5.5). Fifteen patients (12 with idiopathic diabetes insipidus and 3 with Langerhans'-cell histiocytosis) who were followed for a median of 3.8 years (range, 2.7 to 6.5) had persistently normal stalks. Changes in the size of the anterior pituitary region at the time of the last MRI scan are summarized in Tables 1 and 2.

Anterior Pituitary Function

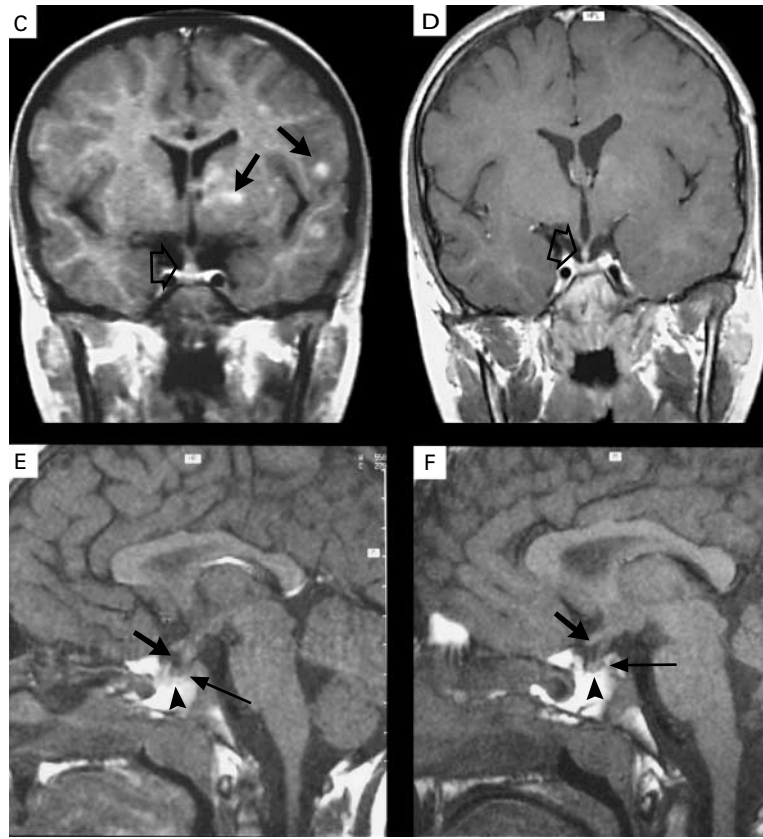
Deficits in anterior pituitary hormones were documented in 48 patients (61 percent) a median of 0.6 year (range, 0.1 to 18.0) after the onset of diabetes insipidus (Table 1). The most frequent abnormality was growth hormone deficiency (47 patients [59 percent]), followed by hypothyroidism (22 patients [28 percent]), hypogonadism (19 patients [24 percent]), and adrenal insufficiency (17 patients [22 percent]). All patients with growth retardation had a serum growth hormone response of less than 5 ng per milliliter after any of the stimulation tests. Serum prolactin concentrations were high (>20 ng per milliliter) at the time of the diagnosis of diabetes insipidus in 16 of 54 patients (30 percent). Twenty of the 41

patients with idiopathic diabetes insipidus (49 percent) had one or more anterior pituitary hormone deficiencies (Table 1).

The median times from the onset of diabetes insipidus to the appearance of the first and final anterior pituitary defects in these 20 patients were 0.6 year (range, 0.1 to 18.0) and 7.7 years (range, 0.1 to 18.0), respectively (Fig. 4). Nine of the 12 patients (75 percent) with Langerhans'-cell histiocytosis had an anterior pituitary hormone deficiency (Table 1) that was first detected a median of 3.5 years (range, 0.1 to 6.0) after the onset of diabetes insipidus. The mean estimated probability that an anterior pituitary hormone defect would develop within six years after the diagnosis of diabetes insipidus was 81 percent for patients with Langerhans'-cell histiocytosis and 49 percent for those with idiopathic diabetes insipidus (Fig. 4). The probability of developing additional defects did not differ significantly between these two groups.

Prognostic Factors

Among the 29 patients with a thickened pituitary stalk, 27 (93 percent) had anterior pituitary hormone deficits, as compared with 6 of the 36 patients (17 percent) with a normal pituitary stalk (odds ratio, 18;



95 percent confidence interval, 4 to 115; $P < 0.001$). Similarly, among the 18 patients with idiopathic diabetes insipidus who had a thickened pituitary stalk, 17 (94 percent) had anterior pituitary hormone deficits, as compared with 2 of the 19 (11 percent) with idiopathic disease who had a normal pituitary stalk (odds ratio, 113; 95 percent confidence interval, 9 to 4956; $P < 0.001$). By contrast, in patients with Langerhans' cell histiocytosis, the risk of an anterior pituitary hormone abnormality was independent of the size of the pituitary stalk. Among patients with idiopathic diabetes insipidus, anterior pituitary hormone deficits were strongly associated with a smaller-than-normal anterior pituitary: 20 of 22 patients with deficits (91 percent) had a smaller-than-normal pituitary, as compared with 3 of 19 patients (16 percent) with a normal-sized pituitary (odds ratio, 54; 95 percent confidence interval, 6 to 606; $P < 0.001$).

DISCUSSION

In our study, most of the 79 patients with central diabetes insipidus who were identified in four pediatric endocrinology units were children. Tumor-associated diabetes insipidus was not diagnosed in children who were younger than five years of age, whereas the familial form of the disorder was diagnosed by the age

of seven in all five affected patients. Forty percent of the patients had symptoms other than polyuria and polydipsia at presentation. We did not find that growth retardation was significantly more common in a single group of patients, in contrast to previous reports indicating that such delays are strongly suggestive of an intracranial tumor as the cause of central diabetes insipidus.^{13,24} In about one fourth of the patients with idiopathic diabetes insipidus, there was a temporal association between a viral infection and the onset of diabetes insipidus, a finding previously reported in isolated cases in neonates.^{10,25}

Many patients did not have posterior pituitary hyperintensity on serial MRI scans, indicating that the absence of hyperintensity, although nonspecific, is a cardinal feature of central diabetes insipidus.¹⁸ In the five patients who did have posterior pituitary hyperintensity at diagnosis,² this feature invariably disappeared during follow-up.²³ Thickening of either the entire pituitary stalk or just the proximal portion was the second most common abnormality on MRI scans. It was helpful in diagnosing idiopathic diabetes insipidus and that associated with germinomas or Langerhans' cell histiocytosis, but it was not specific for any single subtype. Other studies that have reported a thickened pituitary stalk in association with autoim-

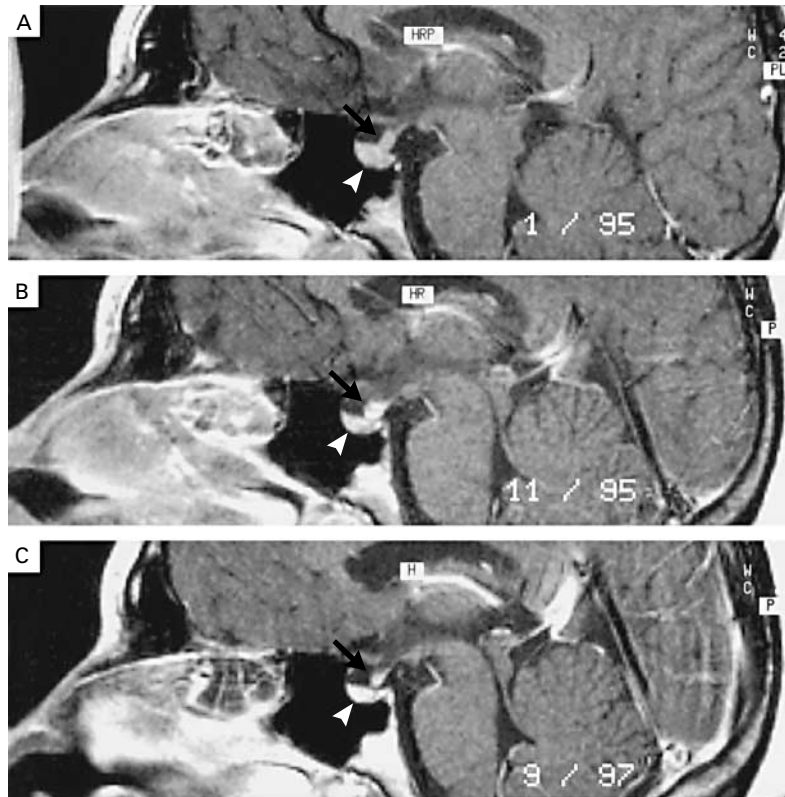


Figure 3. Sagittal T₁-Weighted MRI Scans with Gadolinium Enhancement Obtained in a Patient with Central Diabetes Insipidus Caused by Langerhans'-Cell Histiocytosis.

At presentation (Panel A), the posterior pituitary is not hyperintense (small black arrow), the pituitary stalk is thickened (large black arrow), and the size of the anterior pituitary is normal (white arrowhead). Ten months later (Panel B), there is further thickening of the pituitary stalk (arrow) and a reduction in the size of the anterior pituitary (arrowhead). After approximately two years (Panel C), the pituitary stalk is not as thick (arrow) and there has been no change in the size of the anterior pituitary (arrowhead).

mune or inflammatory disease — termed “lymphocytic infundibuloneurohypophysitis,”⁴ “lymphocytic hypophysitis,”²⁶ or “necrotizing infundibulohypophysitis”²⁷ — have focused on adults with histologic features of lymphocyte and plasma-cell infiltration, fibrosis, and necrosis. Any of these diagnoses seems unlikely in our patients with idiopathic diabetes insipidus, not only because of their young age, but also because 17 of 18 patients with idiopathic disease and a thickened pituitary stalk also had an anterior pituitary hormone deficiency, and some had progressive disease.

Follow-up MRI scans of patients with idiopathic central diabetes insipidus and a thickened pituitary stalk showed a range of changes, from a spontaneous resolution of the abnormality to further enlargement; some had no change. Nonetheless, our findings suggest that a germinoma can be recognized early during follow-up on the basis of an increase in the size of the stalk. In our study, such follow-up led to a bi-

opsy-proven diagnosis of germinoma within a median of 1 year after the diagnosis of central diabetes insipidus, in contrast to the 2.5 years reported for patients evaluated by MRI performed a mean of 1.3 years after the diagnosis of diabetes insipidus.²⁸ In most of the patients with diabetes insipidus who had a normal pituitary stalk on the first MRI examination, there was no change in the size of the stalk during follow-up. However, the protracted interval (median, 1.5 years) between the onset of diabetes insipidus and the first MRI scan may have hidden a rapid change, as suggested by the finding that the size of the stalk returned to normal within a median of 1.2 years in other patients.

The incidence of anterior pituitary hormone deficits, particularly of growth hormone deficiency in patients with idiopathic diabetes insipidus (49 percent), was higher than that reported in other studies.^{13,29} Furthermore, the observation that an anterior pituitary hormone deficit may indicate the presence of a

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TABLE 2. COURSE OF CENTRAL DIABETES INSIPIDUS IN 18 PATIENTS WITH A NORMAL OR THICKENED PITUITARY STALK ON MAGNETIC RESONANCE IMAGING AT PRESENTATION.*

| PATIENT No. | AGE (YR) AT PRESENTATION/ SEX | CAUSE OF DISEASE | STALK SIZE† | | | ENDOCRINE HORMONE DEFICIENCIES IDENTIFIED AT ANY TIME | SIZE OF ANTERIOR PITUITARY ON LAST MRI SCAN |
|-------------|----------------------------------|---------------------------------------------|-------------------------------------|-----------------------|------------------------|-------------------------------------------------------|---------------------------------------------|
| | | | ON FIRST MRI SCAN (AT PRESENTATION) | ON FOLLOW-UP MRI SCAN | ON LAST MRI SCAN | | |
| 1 | 5.2/M | Idiopathic | + | Normal (1.5) | Normal (2.3) | GH | Reduced |
| 2 | 5.5/M | Idiopathic | + | ++ (1.5) | ++ (2.5) | GH and TSH | Reduced |
| 3 | 5.6/M | Idiopathic | + | ± (2.1) | ± (1.4) | GH | Reduced |
| 4 | 7.4/F | Idiopathic | + | ++ (10.3) | ++ (0) | GH and FSH or LH | Reduced |
| 5 | 7.5/F | Idiopathic | + | Normal (1.0) | Normal (3.6) | GH | Reduced |
| 6 | 7.2/M | Idiopathic | + | ++ (2.0) | ++ (4.2) | GH, TSH, and FSH or LH | Reduced |
| 7 | 8.5/F | Idiopathic | + | Normal (1.0) | Normal (2.9) | GH | Reduced |
| 8 | 9.5/M | Idiopathic | + | Normal (1.0) | Normal (3.0) | GH | Reduced |
| 9‡§ | 6.0/M | Idiopathic (inflammatory) | +++ | Normal (5.7) | Normal (0) | GH | Reduced |
| 10§ | 7.5/F | Idiopathic (inflammatory) | + | +++ (1.6) | +++ (1.0) | GH and TSH | Reduced |
| 11§¶ | 8.0/F | Idiopathic (inflammatory) | + | +++ (5.0) | ++ (0.4) | GH and FSH or LH | Reduced |
| 12 | 8.0/F | Germinoma | + | +++ (0.8) | Could not be evaluated | GH and ACTH | Normal |
| 13 | 9.1/F | Germinoma | + | ++ (1.5) | Could not be evaluated | GH and TSH | Increased |
| 14 | 7.1/F | Langerhans ² -cell histiocytosis | + | Normal (5.1) | Normal (2.5) | GH | Reduced |
| 15 | 6.4/M | Idiopathic | Normal | + (3.0) | + (1.1) | None | Reduced |
| 16 | 11.8/M | Idiopathic | Normal | + (1.0) | + (0.3) | None | Normal |
| 17 | 11.1/M | Germinoma | Normal | + (0.5) | +++ (0.5) | None | Increased |
| 18 | 19.8/M | Langerhans ² -cell histiocytosis | Normal | ++ (0.2) | + (2.6) | None | Normal |

*MRI denotes magnetic resonance imaging, GH growth hormone, TSH thyrotropin, FSH follicle-stimulating hormone, LH luteinizing hormone, and ACTH corticotropin.

†A normal stalk was defined as one that was less than 3.0 mm thick. A single plus sign indicates a thickness of 3.0 to 4.5 mm, two plus signs a thickness of 4.6 to 6.5 mm, three plus signs a thickness of more than 6.5 mm, and a plus-minus sign a stalk size that was smaller than it had been on the previous measurement but that was still more than 3.5 mm. Values in parentheses are the intervals (in years) since presentation, in the case of the follow-up MRI scan, or since the follow-up scan, in the case of the last MRI scan.

‡This patient had MRI evidence of diffuse inflammatory infiltrates in the brain.

§In this patient, the findings on pituitary-stalk biopsy were compatible with the presence of an inflammatory process.

¶This patient was treated with prednisolone during follow-up.

||This patient was treated with prednisolone and vinblastine during follow-up.

tumor in patients with diabetes insipidus^{13,24} was not confirmed by our data. In idiopathic diabetes insipidus, growth hormone deficiency can develop soon after the onset of disease, with additional pituitary defects becoming evident later on. Our finding of a longer median interval between the diagnosis of diabetes insipidus and the detection of the first anterior pituitary hormone deficit in patients with Langerhans²-cell histiocytosis than in patients with idiopathic diabetes insipidus (3.5 years vs. 0.6 year) confirms our recent findings³⁰ and could be related to a reactivation of the disease, the effects of treatment, or perhaps both.

MRI evidence of a progressive reduction in the size of the anterior pituitary was associated with a higher risk of an additional endocrine defect. This decrease in size, as suggested by a recent report,²⁸ may be a consequence of vascular damage^{8,31} or a deficiency of hypothalamic hormones. MRI evidence of an increase in the size of the anterior pituitary with thickening of the stalk was strongly associated with the presence of a germinoma.

In conclusion, children and young adults with acquired central diabetes insipidus, especially those with a thickened pituitary stalk and a reduction in the size

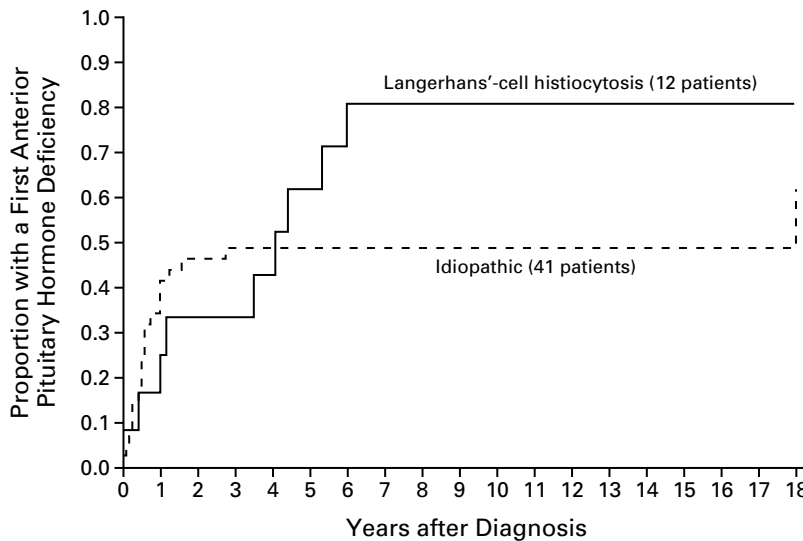


Figure 4. Cumulative Probability of the Development of an Anterior Pituitary Hormone Deficiency during Follow-up in 41 Patients with Idiopathic Central Diabetes Insipidus and 12 Patients with Central Diabetes Insipidus Associated with Langerhans'-Cell Histiocytosis.

of the anterior pituitary, are prone to the development of a growth hormone deficiency or a deficiency of another anterior pituitary hormone. The high frequency (52 percent) of cases of idiopathic central diabetes insipidus in our study most likely reflects our incomplete knowledge of the causes of this disease. The term “lymphocytic infundibuloneurohypophysitis,” which is used to describe cases of central diabetes insipidus in adults with a thickened pituitary stalk, is applicable to childhood cases only when the pituitary stalk is transiently or persistently thickened, the posterior pituitary is not hyperintense on MRI, and the size of the anterior pituitary is normal. The term “lymphocytic infundibulohypophysitis” would be more appropriate to describe patients with anterior pituitary hormone deficiencies. A progressive increase in the size of the anterior pituitary should alert physicians to the possibility that a germinoma is present, whereas a decrease can suggest the presence of an inflammatory or autoimmune process. Biopsy should be reserved for patients with progressive thickening of the pituitary stalk, since spontaneous recovery may occur in patients without this feature.

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