THICKENED PITUITARY STALK WITH CENTRAL DIABETES INSIPIDUS: REPORT OF THREE CASES

Keh-Chau Sheen, Ching-Chung Chang, Tien-Chun Chang, and Hon-Man Liu

Abstract: Diabetes insipidus of central origin usually results from lesions in the hypothalamic neurohypophyseal system. Lymphocytic infundibuloneurohypophysis is an uncommon cause. Cases of lymphocytic infundibuloneurohypophysisitis with thickening of the pituitary stalk and enlargement of the neurohypophysis with no hyperintense signal in the posterior pituitary have been reported. Reported cases presenting with isolated thickening of the pituitary stalk are very rare. We report three such cases, one in a nulliparous woman and the other two in men. Magnetic resonance (MR) imaging in these patients revealed isolated thickening of the pituitary stalk, loss of the hyperintense signal of the posterior pituitary, and an adenohypophysis of normal size. All cases had abnormal nodular infundibular enlargement. One male patient had hypogonadism; the other patients showed no sign of adenohypophyseal deficiency on stimulation test. Serial follow-up MR imaging revealed that all three patients had persistent thickening of the pituitary stalk. Diabetes insipidus was controlled by the administration of desmopressin acetate in all patients.

Diabetes insipidus is an uncommon disorder affecting approximately three in 100,000 people [1], and is characterized by the excretion of diluted urine (< 300 mOsm/kg) at more than 3 L per day (> 50 mL·kg⁻¹·d⁻¹), with a specific gravity of less than 1.01 [2]. The most common causative defect is central diabetes insipidus, which most commonly results from lesions in the hypothalamic-neurohypophyseal axis. The causes of central diabetes insipidus include surgery, head trauma, infection, tumors [3], hematologic malignancies [4], granulomas [5], idiopathic inflammatory processes [6], congenital malformation, genetic mutation [7], and brain hypoxia or ischemia [8].

Lymphocytic infundibuloneurohypophysisitis is an uncommon medical problem. Cases of lymphocytic infundibuloneurohypophysisitis with normal adenohypophysis, thickening of the pituitary stalk, and enlargement of the neurohypophysis without the hyperintense signal of the posterior pituitary have been reported [9], but reported cases presenting with isolated prominent thickening of the pituitary stalk are very rare. We describe three patients with thickened pituitary stalk who presented with diabetes insipidus. These patients all had clinical and radiologic evidence of central diabetes insipidus. Magnetic resonance (MR) imaging revealed thickening of the pituitary stalk, loss of the normal high-intensity signal of the posterior pituitary, and a normal-size adenohypophysis. All had abnormal nodular infundibular enlargement. One patient had hypogonadism; the others showed no sign of adenohypophyseal deficiency on stimulation test.

This disorder is not associated with either pregnancy or the postpartum period in female patients, and has no sex predilection. Serial follow-up MR imaging without and with gadolinium enhancement in all three patients revealed persistent swelling of the pituitary.
stalk. All patients had persistent diabetes insipidus. The clinical picture and serial examinations suggested that these patients probably had lymphocytic infundibuloneurohypophysitis.

Case Reports

Case 1

This 25-year-old male had suffered from polydipsia and polyuria for 4 years, with sudden onset of symptoms. His body weight increased from 53 to 70 kg during the initial 6 months. He used ice-cold water to quench thirst. His urine volume was about 10 L per day. Hyperglycemia was noted, and diabetes mellitus was the initial tentative diagnosis. His condition progressed slowly, with increased body weight. Heat intolerance with decreased sweating developed later. MRI imaging of the sella turcica on May 10, 1996, revealed a slight prominence of the upper part of the pituitary stalk. He was referred to our hospital 2 months later.

On admission, his blood pressure was 150/100 mm Hg, hemoglobin was 13.7 g/dL, blood glucose concentration was 232 mg/dL, HbA1c was 8.1%, body weight was 80 kg, and serum sodium concentration was 144 mEq/L. Urine specific gravity was less than 1.01 and his daily urine volume was 7 to 9 L. Plasma osmolality was 291 mOsm/kg and urine osmolality was 75 mOsm/kg. Water deprivation and desmopressin test revealed central diabetes insipidus. Ophthalmoscopic and visual examinations were normal. The carcinoembryonic antigen (CEA) concentration was not elevated. MRI imaging of the sella turcica on July 6, 1996, revealed loss of the normal posterior pituitary bright signal intensity, abnormal nodular enlargement, and thickening of the pituitary stalk (sagittal width x coronal width, 5 mm x 6 mm; Fig. 1). Laboratory tests revealed the following hormone concentrations: follicle-stimulating hormone (FSH) 0.9 mIU/mL, luteinising hormone (LH) 1.3 mIU/mL, estradiol 34 pg/mL, testosterone 1.34 ng/mL, growth hormone (GH) 0.06 μg/L, dehydroepiandrosterone sulfate (DHEAS) 12.2 μmol/L, cortisol (at 08:00) 23.9 μg/dL, and adrenocorticotrophic hormone (ACTH) (at 08:00) 30.3 pg/mL. Thyroid function test revealed a triiodothyronine (T3) concentration of 136 ng/dL, a thyroxine (T4) concentration of 9.15 μg/dL, a free T4 concentration of 1.3 ng/dL, and a free thyroid-stimulating hormone (TSH) concentration of 1.85 μU/mL. In response to 400 μg intravenous thyrotropin-releasing hormone (TRH), the serum concentrations of TSH at 0, 15, 30, 60, and 120 minutes were 1.26, 11.07, 10.60, 6.26, and 3.32 μU/mL, and of prolactin were 4.4, 16.4,

Fig. 1. Case 1. A) Sagittal T1-weighted image without gadolinium administration and B) coronal T1-weighted image with gadolinium administration show nodular enlargement and thickening of the pituitary stalk (bigger arrows), and normal adenohypophysis (arrowheads). Three years later: C) sagittal T1-weighted image without gadolinium administration and D) coronal T1-weighted image with gadolinium administration reveals that these abnormalities persisted.
Case 2
This 25-year-old nulliparous woman was hospitalized on October 20, 1998 because of polyuria and polydipsia that had developed one-and-a-half months earlier. Her urine volume was about 10 L per day. Her blood pressure was 120/80 mmHg, hemoglobin concentration was 13.0 g/dL, blood glucose concentration was 90 mg/dL, serum sodium concentration was 147 mmol/L, and urine sodium concentration was 46 mmol/L. Plasma osmolality was 296 mOsm/kg and urine osmolality was 158 mOsm/kg. No pretilial pitting edema was noted.

The patient had been admitted to another hospital on October 2, 1998. Water deprivation and pitressin test revealed central diabetes insipidus. Nasal desmopressin acetate was administered with significant response and the urine volume decreased to about 5 L per day. However, she suffered from worsened thirst after intranasal use of desmopressin acetate. Edema of bilateral lower extremities and a body weight gain of 1.5 kg developed. She was admitted to our hospital. Desmopressin acetate was discontinued and the urine volume increased to 15 L per day. Repeat water deprivation and desmopressin test still showed central diabetes insipidus. MR imaging of the sella turcica showed enlargement and thickening of the pituitary stalk (sagittal width x coronal width, 3 mm x 4 mm), and the normal bright signal intensity of the posterior lobe was lost (Fig. 2).

Laboratory tests revealed the following hormone concentrations: FSH 5.8 mU/mL, LH 1.1 mU/mL, estradiol 20 pg/mL, progesterone 1.0 ng/mL, androstenedione 3.16 nmol/L, GH 1.2 µg/L, DHEA-SO4 6 µmol/L, cortisol (at 08:00) 64 µg/dL, and ACTH (at 08:00) 96.7 pg/mL. Thyroid function test revealed a T4 concentration of 174 ng/dL, a T4 concentration of 11.6 µg/dL, a free T4 concentration of 1.4 ng/dL, and a TSH concentration of 3.3 µU/mL. In response to 400 µg intravenous TRH, the serum concentrations of TSH at 0, 15, 30, 60, and 120 minutes were 2.11, 11.80, 14.10, 9.70, and 4.12 µIU/mL, and of prolactin were 11.7, 37.7, 35.7, 21.6, and 13.1 ng/mL. After 100 µg intravenous LHRH, the serum LH concentrations at 0, 30, 60 and 120 minutes were 2.6, 14.4, 10.7, and 6.8 µIU/mL, and the FSH concentrations were 6.0, 11.1, 17.7, and 10.7 µIU/mL. After 0.2 mL intramuscular cosynorotin (20 U ACTH) was given twice per day on Day 1 and Day 2, the serum cortisol concentrations at 0, 24, and 48 hours were 15.39, 16.2, and 90.6 µg/dL, respectively. LHRH, TRH test, and cortrosyn stimulation test revealed normal responses. Desmopressin acetate (0.1 mg po q8h) was restarted and the urine volume decreased to 1.2 L per day. Follow-up MR imaging on August 30, 1999, still showed nodular enlargement and thickening of the pituitary stalk. She continued desmopressin acetate replacement therapy due to the persistence of diabetes insipidus.
loss of the normal posterior pituitary bright signal intensity, abnormal nodular enlargement, and thickening of the pituitary stalk (sagittal width x coronal width, 10 mm x 6 mm); the anterior lobe was of normal size, shape, and enhancement (Fig. 3).

The patient was treated with desmopressin acetate 10 µg bid intranasally. His daily urine volume decreased to 3.4 L. Hypogonadism was treated with chorionic gonadotropin. Follow-up MR imaging on September 27, 1998, March 23, 1999, and September 22, 1999, still showed nodular enlargement and thickening of the pituitary stalk. The diabetes insipidus persisted and was medically controlled with desmopressin acetate nasal solution.

Discussion

Idiopathic diabetes insipidus accounts for 10 to 30% of cases of central diabetes insipidus [9]. Several studies have demonstrated the utility of MR imaging in the evaluation of hypothalamic-pituitary disorder [3, 7, 10, 11]. MR imaging has shown that the normal neurohypophysis generates a hyperintense signal on T1-weighted images, which was observed in 90 to 100% of healthy subjects and was not seen in patients with idiopathic or secondary diabetes insipidus [12]. MR imaging of the normal pituitary demonstrates a hyperintense posterior lobe that is as bright as fat on T1-weighted images. Because the pituicytes in the posterior lobe contain variable amounts of both lipid and neurosecretory granules, depending on the level of antidiuretic hormone synthesis and release, the source of the hyperintense MR signal in the normal neurohypophysis has been controversial [13, 14]. However, the suggestion that the absence of this hyperintense signal is related to interruption of synthesis or axonal transport of vasopressin neurosecretory granules along the hypothalamic-infundibular-neurohypophyseal pathway is probably reasonable [10].

The combination of a thickened pituitary stalk and the absence of posterior pituitary signal hyperintensity has been previously reported in central diabetes insipidus [9, 12]. The upper limit of normal for the width of the pituitary infundibulum is 3.5 mm near the median eminence and 2.8 mm at its midpoint [12]. The differential diagnosis of a thickened pituitary stalk includes...
Langerhans cell histiocytosis [12], lymphocytic infundibuloneurohypophyseitis [9], tuberculosis [5], sarcoidosis [15], germinoma [3], and infiltration from adjacent neoplasm and metastasis. The prevalence of metastasis to the pituitary gland ranged from 1.8 to 12% in different series [3]. The most common type of metastasis is from breast cancer, followed by carcinoma of the gastrointestinal system.

Transient diabetes insipidus has also been reported in tuberculous meningitis. Diabetes insipidus patients with tuberculosis and sarcoidosis usually have an abnormal chest film [15]. Pineal germinoma is the most common intracranial tumor associated with central diabetes insipidus in children, which characteristically shows a pineal mass with cerebrospinal fluid metastasis and parainflamnnd syndrome [3]. MR imaging can clearly demonstrate a thickened upper pituitary stalk and a lobulated pineal mass.

The most important differentiation in diagnosis of a thickened pituitary stalk is Langerhans cell histiocytosis. In this disease, 56% had diabetes insipidus, 25% had skin manifestations, 15% had pulmonary infiltrate, and 15% had otitis media [3]. Further studies, such as chest roentgenography, bone scanning, or temporal bone computerized tomography, should be useful in establishing the diagnosis.

Central nervous system involvement as a complication of systemic histiocytosis is not uncommon. It is usually a manifestation of systemic disease with pituitary involvement or due to extension of the process from adjacent areas. A primary intraparenchymal origin of this disease confined to the pituitary gland is considered extremely rare [3]. Our three patients had no signs of Langerhans cell histiocytosis in brain parenchyma or other tissues, which is often present in this disorder.

Lymphocytic infundibuloneurohypophyseitis was first described in 1993 by Imura et al [9]. In their series, patients showed an absence of the hyperintense signal of the neurohypophysis on T1-weighted images. The anterior pituitary gland was normal. No patient had symptoms or signs of anterior hormone deficiency [9]. However, all patients had a thickened pituitary stalk and diabetes insipidus. Microscopic examination of biopsy specimens revealed inflammatory infiltrates composed of lymphocytes and plasma cells with scattered eosinophils, neutrophils, and histiocytes. Most of
the infiltrating lymphocytes were T-cells. One of our patients had hypogonadism; the others showed no sign of adenohypophysial deficiency on stimulation test. Lymphocytic infundibuloneurohypophysitis was diagnosed in two of our patients based on evidence of a thickened pituitary stalk, a normal-size anterior pituitary gland on MR imaging, and the diagnosis of diabetes insipidus. However, the third patient had hypogonadism, unlike any of the patients in the series of Imura et al [9].

Teelucksingh et al reported that pituitary stalk enlargement occurred in idiopathic central diabetes insipidus, and persisted for months to years before eventually disappearing [16]. Among the 17 cases of central diabetes insipidus reported by Imura et al [9], nine had thickening of the pituitary stalk and enlargement of the neurohypophysis. In the remaining eight patients, the pituitary stalk and the neurohypophysis were normal. The abnormalities of thickening and enlargement were seen on MR imaging only in patients who had had diabetes insipidus for less than 2 years [9]. All of our patients had isolated thickening of the pituitary stalk and no evidence of tuberculosis, sarcoidosis, or histiocytosis. Cases 1 and 3 had persistent nodular enlargement and thickening of the pituitary stalk for more than 2 or 4 years.

The natural course of this disorder is self-limited and Imura et al suggested surgical intervention was not indicated [9]. However, our patients did not show the same disease course as in previous reports. At present, no definite criteria exist about how to recognize this disease without histologic confirmation, and inadequate data is available to establish guidelines for clinical and imaging follow-up in such patients [17, 18].

Care must be taken to distinguish lymphocytic infundibuloneurohypophysitis from lymphocytic adenohypophysitis. Lymphocytic adenohypophysitis is an autoimmune disorder of the pituitary gland [19, 20]. This pathologic entity was first described in 1962 by Goudie and Pinkerton [21]. The disease shows a striking female predilection of approximately 8:5:1 and commonly affects young women during the antepartum or postpartum period [19]. Some of these patients have been reported to have organ-specific and other autoimmune disorders, such as Hashimoto's disease and silent thyroiditis, idiopathic adenitis, atrophic gastritis, and lymphocytic parathyroiditis [22]. Histologic study showed a lymphoplasmacytic infiltrate with varying numbers of neutrophils, macrophages, and eosinophils. Cemeroğlu et al reported that 13% of lymphocytic adenohypophysitis cases had diabetes insipidus [23]. The direct involvement of the pituitary stalk and/or neurohypophysis with inflammatory process resulting in destruction of hypothalamic pathways was documented by biopsy. A few previous reports have described patients presenting with diabetes insipidus whose pituitary gland specimen revealed lymphocytic infiltration of the adenohypophysis, neurohypophysis, and infundibulum [24, 25]. The anterior pituitary function was not greatly damaged and no hormonal replacement therapy was needed in these patients. Their MR images always showed swelling of the whole pituitary gland, loss of the normal high-intensity signal of the posterior pituitary, and/or thickening of the pituitary stalk. Desmopressin acetate was administered only for patients with diabetes insipidus. Though lymphocytic infiltration of the pituitary stalk resulting in central diabetes insipidus was suggested to be a separate disease that tends not to involve the anterior pituitary gland [9], autoimmune processes may not be restricted to adenohypophysitis or neurohypophysis. Our third patient, whose MR imaging showed abnormal nodular enlargement, thickening of the pituitary stalk, and a normal-size anterior pituitary lobe, had hypogonadism and diabetes insipidus. This presentation is different from that described by Koshiyama et al [24] and Goudie and Pinkerton [21], and suggests the existence of a variant form of lymphocytic infundibuloneurohypophysitis.

The present three cases are interesting because of the findings of isolated thickening of the pituitary stalk, which is very rare and could be confused with other diseases. Although the diagnosis of lymphocytic infundibuloneurohypophysitis mainly depends on histologic findings, MR imaging provides an alternative method for the diagnosis of such cases. In addition, we suggest that repeated MR imaging every 6 months in the following 2 years provides a better follow-up for this self-limiting disease.

References


