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Thickened Pituitary Stalk on MR Images in Patients with Diabetes Insipidus and Langerhans Cell Histiocytosis

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The MR images of four female patients with acute onset of central diabetes insipidus and pathologically confirmed Langerhans cell histiocytosis were evaluated retrospectively for evidence of lesions in the hypothalamic-pituitary axis. The examinations were conducted on a 1.5-T MR system with thin-section sagittal and coronal T1-weighted (short TR/short TE) and T2-weighted (long TR/long TE) images. Three patients underwent T1-weighted MR after IV administration of gadopentetate dimeglumine. Compared with 20 normal subjects who were evaluated with the same MR protocol, three of the four patients had a symmetrically thickened pituitary stalk that demonstrated homogeneous signal enhancement following contrast administration. The high signal intensity of the posterior lobe, which was seen in normal subjects on T1-weighted sagittal images, was absent in all four patients. Two patients had associated abnormalities on either chest films or imaging studies of the temporal bone and two patients had isolated CNS Langerhans cell histiocytosis.

The combination of a thickened pituitary stalk and absent posterior pituitary hyperintensity, while nonspecific for Langerhans cell histiocytosis, should nevertheless prompt further studies, such as chest films, bone scanning, or temporal bone CT, to attempt to narrow the differential diagnosis. Gadopentetate dimeglumine, in particular, may be a useful adjunct in the MR examination of the patient with diabetes insipidus.

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Histiocytosis X is a term coined by Lichtenstein [1] in 1953 to include eosinophilic granuloma of bone, Hand-Schüller-Christian disease, and Letterer-Siwe disease. More recently, the involvement of a dendritic cell of bone marrow origin has been demonstrated as the common pathologic element, leading to the name Langerhans cell histiocytosis [2]. Although isolated Langerhans cell histiocytosis of the CNS is rare, CNS involvement is not uncommon as part of a systemic process [3, 4]. This usually takes the form of neuroendocrine disturbances involving the hypothalamic-neurohypophyseal axis (Gagel granuloma) [5–7].

We report the MR findings in four patients with diabetes insipidus who were investigated for evidence of pituitary-hypothalamic disease.

Materials and Methods

Four female patients presenting with diabetes insipidus underwent MR imaging of the pituitary-hypothalamic region (Table 1). The diagnosis of Langerhans cell histiocytosis was confirmed pathologically in each case, and clinical features consistent with diabetes insipidus were also noted. Two of the patients had evidence of systemic involvement with Langerhans cell histiocytosis. MR imaging was performed on a 1.5-T superconductive imager (General Electric Co., Milwaukee, WI) using standard protocol. Spin-echo images were acquired using a head coil, 256 × 256 matrix, 20-cm field of view, and 3-mm-thick sections. T1-weighted images, 600/20/4 (TR/TE/excitations), without intersection gap and T2-weighted axial and coronal images, 2000/20–80/1 or 2000/40–80/1, with a 50% interslice gap were obtained. In three patients, T1-weighted images were obtained after IV administration of gadopentetate dimeglumine.

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TABLE 1: Summary of Clinical Symptoms and MR Findings in Four Patients with Langerhans Cell Histiocytosis

Case No.	Age (years)	Sex	Initial Clinical Symptoms	MR Findings of Stalk	Associated Findings	Chest Film	Diagnosis	Follow-up Clinical Course
1	3	F	Acute onset of DI, skin rash, hepatosplenomegaly at age 1	7/86: symmetrically thickened; SW = 3 mm; CW = 4 mm 11/86: SW = 2 mm; CW = 3 mm 6/88: SW = 5 mm; CW = 6.5 mm 8/88: SW = 4 mm; CW = 5 mm; stalk enhanced normally after gadopentetate dimeglumine administered 9/88: SW = 0.35 mm; CW = 0.35 mm	Absence of high signal intensity of posterior pituitary on T1-weighted images	Interstitial infiltrate at age 1	Skin biopsy: Langerhans cell histiocytosis	600 rad (60 Gy) local radiation to hypothalamus and stalk, 9/86; chemotherapy from 9/86 to 2/87; DI was unalleviated
2	16	F	Acute onset of DI, mastoid pain	8/85: symmetrically thickened; SW = 7 mm; CW = 6 mm 7/86: thickened hypothalamus and median eminence of pituitary stalk; SW = 17 mm; CW = 16 mm 8/87: SW = 17 mm; CW = 11 mm 9/88: SW = 11 mm; CW = 6 mm	Absence of high signal intensity of posterior pituitary on T1-weighted images	Normal	Temporal bone biopsy: Langerhans cell histiocytosis	1000 rad (10 Gy) local radiation to stalk and hypothalamus, 8/86; DI persisted without alleviation; there was evidence of arrest of puberty and decreased growth hormone; additional 2000 rad (20 Gy) local radiation, 7/87
3	29	F	Acute DI	Minimal asymmetric thickening; stalk enhanced homogeneously with administration of gadopentetate dimeglumine 1: SW = 5 mm; CW = 4 mm 2: SW = 2.8 mm; CW = 3 mm	Absence of high signal intensity of posterior pituitary on T1-weighted images	Normal	Open biopsy of stalk: Langerhans cell histiocytosis	2200 rad (22 Gy) local radiation to hypothalamus and stalk; DI was unalleviated
4	57	F	Acute DI	Partially empta sella; symmetrically thickened stalk; stalk and hypothalamic nodule enhanced after administration of gadopentetate dimeglumine: SW = 5 mm; CW = 4 mm	Absence of high signal intensity of posterior pituitary on T1-weighted images	Normal	Open biopsy of hypothalamic nodule: Langerhans cell histiocytosis	Irradiation to be scheduled

Note.—DI = diabetes insipidus; SW = sagittal width; CW = coronal width.

Twenty normal patients were evaluated by the same MR protocol to determine the normal size and shape of the infundibulum.

Case Reports

Case 1

A 5-month-old girl was admitted to the University of California, San Francisco, Medical Center in July 1986 for a skin rash and persistent bilateral otitis media. A chest film showed increased pulmonary vascular markings with peribronchial cuffing. Laboratory studies revealed hypogammaglobulinemia. Skin, gingival, and rectal biopsies were consistent with the diagnosis of Letterer-Siwe disease. Trimethoprim sulfate, vinblastine, and cortisone cream therapy was initiated. Although the skin lesions had cleared and the chest films were normal, diabetes insipidus developed 1 year later. An MR scan in July 1986 revealed a slightly thickened infundibulum and absence of the normal high signal intensity in the posterior lobe (Figs. 1A and 1B). Vinblastine methotrexate, cyclophosphamide, and prednisone chemotherapy was then initiated. Desmopressin acetate was given intranasally to treat the diabetes insipidus. Radiation therapy (600 rad [6 Gy]) to the hypothalamus was initiated in September 1986.

The pituitary infundibulum appeared normal on MR studies performed in November 1986. However, no improvement was noted in the diabetes insipidus. Chemotherapy was discontinued in February 1987. Follow-up MR studies in February and December 1987 re-

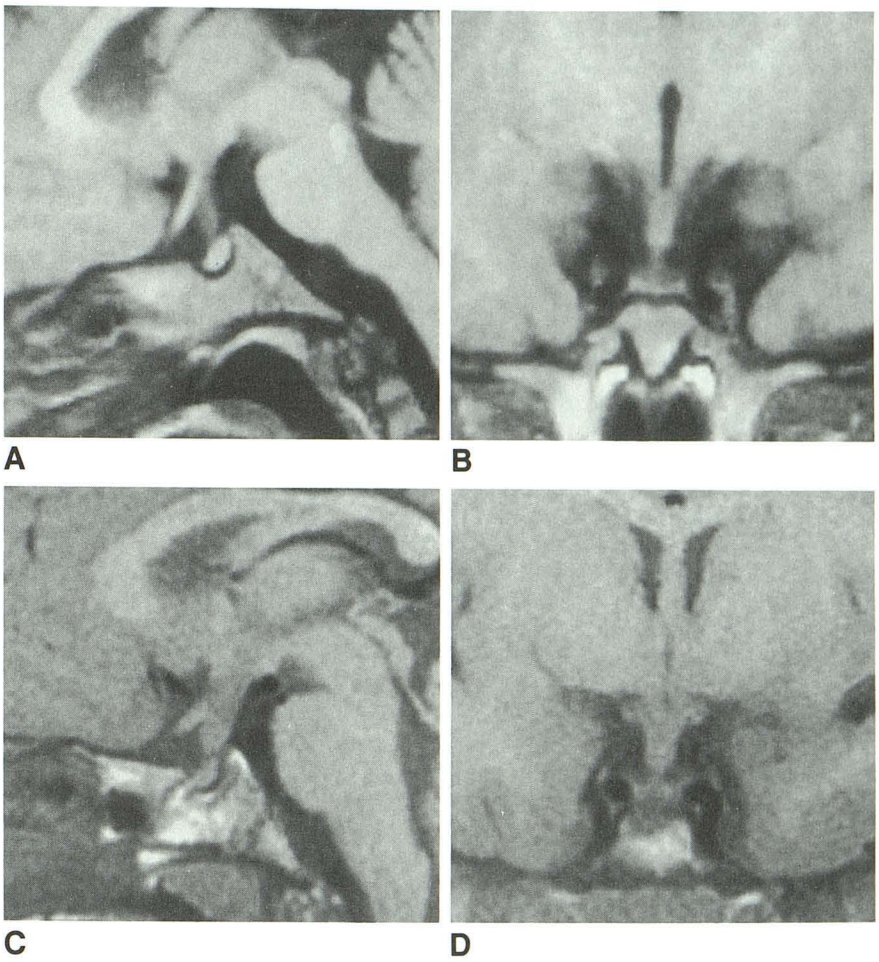

Fig. 1.—Case 1.

***A* and *B*, Sagittal (*A*) and coronal (*B*) T1-weighted images, 600/20, show a symmetric slightly thickened pituitary stalk and absence of normal high signal intensity in posterior pituitary lobe.**

***C* and *D*, Sagittal (*C*) and coronal (*D*) T1-weighted images, 600/20, 2 years later reveal more markedly thickened pituitary stalk (coronal width, 6.5 mm) and absence of high signal intensity in posterior pituitary lobe.**

vealed a normal pituitary infundibulum. However, the clinical diabetes insipidus was unchanged. Routine follow-up MR studies in June 1988 again showed a more markedly thickened pituitary infundibulum (6.5 mm on coronal T1-weighted images) (Figs. 1C and 1D). No further chemotherapy or radiation therapy was given. MR studies 2 months (including gadopentetate dimeglumine enhancement) and 4 months later revealed a progressive decrease in the thickness of the stalk. However, diabetes insipidus persisted.

Case 2

A 14-year-old girl had had sudden onset of diabetes insipidus and pain in the right mastoid region. Initial chest film studies were normal, but an osteolytic lesion was noted in the right temporal bone on skul films. Skeletal surveys revealed an osteolytic lesion in the right femur. MR in August 1985 showed a symmetrically thickened pituitary stalk and a destructive lesion in the right temporal bone. The normal bright signal on T1-weighted MR of the posterior lobe of the pituitary gland was not seen (Figs. 2A and 2B). Diagnosis of Langerhans cell histiocytosis was confirmed by biopsy of the lesion in the femur and mastoid. The hypothalamic region was irradiated with 1000 rad (10 Gy). Intranasal desmopressin acetate controlled her diabetes insipidus. The femoral lesion responded well to chemotherapy. Clinical evidence of growth hormone deficiency was seen about 1 year later. MR in July 1986 revealed a massive thickening of hypothalamus and median eminence of the pituitary stalk (17 mm) (Figs. 2C and 2D). An additional 2000 rad (20 Gy) of local radiation was given. Follow-up MR studies in August 1987 and September 1988 showed slight reduction in the size of the stalk. However, the diabetes insipidus persisted.

Case 3

A 29-year-old woman who had been in good health previously suddenly developed diabetes insipidus. Physical examination and chest film studies were normal. MR revealed a mildly thickened pituitary infundibulum with slight irregularity (Fig. 3). Homogeneous enhancement of the pituitary infundibulum was noted after administration of gadopentetate dimeglumine. Biopsy of the pituitary stalk revealed Langerhans cell histiocytosis. Desmopressin acetate and chemotherapy were initiated. A dose of 2200 rad (22 Gy) was given to the hypothalamic region; the most recent MR follow-up showed a normal-sized pituitary stalk, but diabetes insipidus persisted.

Case 4

A 57-year-old woman had acute onset of diabetes insipidus. Physical examination and chest films were normal. An MR study showed a moderately thickened pituitary stalk with a partially empty sella. The normal high signal intensity in the posterior pituitary lobe was absent. The pituitary stalk enhanced after administration of gadopen-

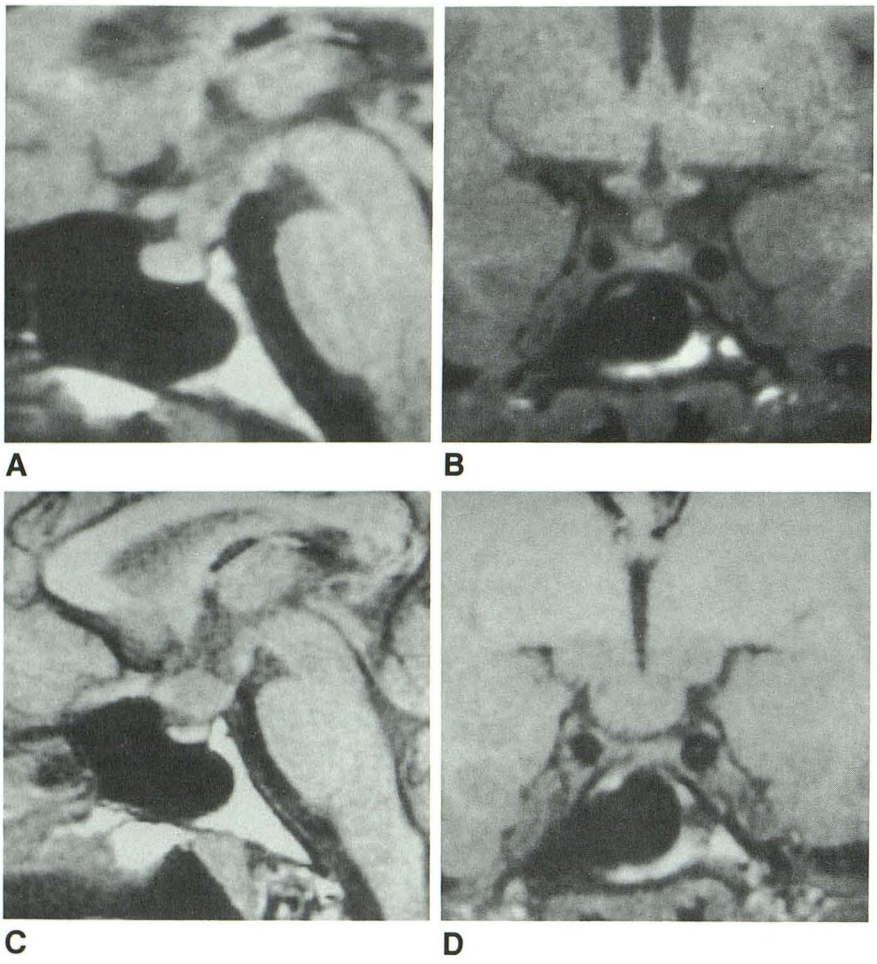

Fig. 2.—Case 2.
A and *B*, Sagittal (*A*) and coronal (*B*) T1-weighted images, 600/20, show symmetric but moderately thickened pituitary stalk and absence of normal high signal intensity in posterior pituitary lobe.
C and *D*, Sagittal (*C*) and coronal (*D*) T1-weighted images, 600/20, 1 year later reveal symmetric but massive thickening of hypothalamus and median eminence of pituitary stalk (coronal width, 16 mm) and absence of high signal intensity in posterior pituitary lobe.

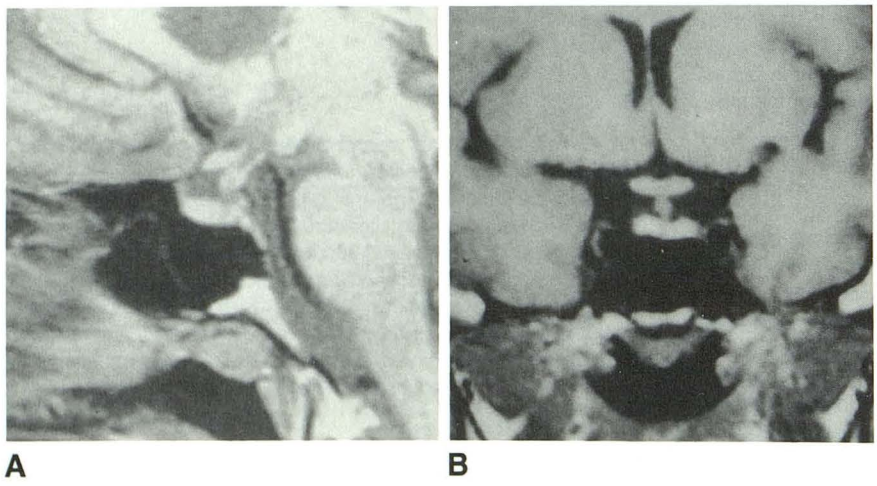

Fig. 3.—Case 3.
A and *B*, Sagittal (*A*) and coronal (*B*) T1-weighted images, 600/20, show slightly asymmetrically thickened stalk and absence of high signal intensity in posterior pituitary lobe.

Fig. 4.—Case 4.
Coronal T1-weighted image, 600/20, after gadopentetate dimeglumine shows small enhancing nodule (*arrowheads*) just above median eminence. in posterior pituitary lobe.
Nodule was greenish in appearance during surgery; histologic study revealed Langerhans cell histiocytosis.

tetate dimeglumine (Fig. 4). An enhancing nodule was noted in the hypothalamus anterosuperior to the median eminence. Biopsy of the nodule yielded a diagnosis of Langerhans cell histiocytosis. The patient was discharged on desmopressin acetate to control the diabetes insipidus. Local radiation therapy was planned.

Results

The upper limit in the width of the pituitary infundibulum is 3.5 mm near the median eminence and 2.8 mm at its midpoint, as shown in a review of normal patients. Three of the four patients in this series had symmetrically thickened stalks (Figs. 1, 2, and 4). In the fourth patient the stalk was asymmetrically thickened (Fig. 3). Intense and homogeneous enhancement of the thickened stalks was noted in the three patients who received gadopentetate dimeglumine. The high signal intensity of the posterior pituitary lobe, commonly seen on T1-weighted sagittal images, was absent in all patients. No "ectopic" bright spot was noted in the hypothalamus. Lytic lesions of the temporal bone were noted on plain skull films as well as on CT and MR in one patient (case 2). An abnormal chest film showing interstitial infiltration was noted in one patient at the age of 1 year (case 1). In one patient (case 3) the abnormalities were limited to thickening of the pituitary stalk. A thickened stalk with an abnormally enhanced hypothalamic nodule was noted in one patient (case 4).

Discussion

Diabetes insipidus occurs either as a result of deficient secretion of the antidiuretic hormone, arginine vasopressin, from the hypothalamus (neurogenic diabetes insipidus), or from an inadequate response to this peptide at the level of the renal tubules (nephrogenic diabetes insipidus). Arginine vasopressin is synthesized within the supraoptic and paraventricular nuclei of the hypothalamus, linked to a specific carrier protein neurophysin, and then transported by axoplasmic flow to the posterior lobe of the pituitary gland. Subsequently, the hormone is released by exocytosis at the end terminal of the axon into the perivascular spaces of posterior pituitary gland.

Fujisawa et al. [8, 9] have suggested that the high signal intensity within the posterior lobe of the pituitary gland on short TR/short TE MR images is caused by neurosecretory granules containing arginine vasopressin and neurophysin. Another possibility is that the hyperintensity is related to intracellular lipid droplets contained in the glial cell pituicytes of the posterior lobe [10]. Histologic studies with lipid-specific marker and electron microscopy data indicate that the posterior lobe, unlike the anterior pituitary, has a high lipid content [10]. Since 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, it is quite conceivable that the two theories are not mutually exclusive. Further studies are needed to resolve this issue.

Hyperintensity of the posterior lobe was observed in 90% [11] to 100% [8] of healthy subjects, but was not seen in the posterior pituitary of patients with diabetes insipidus [9]. Similarly, the hyperintense signal was not observed in the posterior lobe or hypothalamus of the four patients in this study, each of whom had a thickened pituitary stalk and a clinical finding of diabetes insipidus.

In a review of 180 patients with multifocal eosinophilic granuloma, 56% had diabetes insipidus, 25% had skin manifestations, 15% had pulmonary infiltrate, and 15% had otitis media [12]. Radiographic evaluation of the lungs and temporal bone therefore is useful in establishing the diagnosis of Langerhans cell histiocytosis in patients with acute diabetes insipidus (cases 1 and 2).

A thickened stalk in the absence of other lesions was noted in two of our patients (cases 3 and 4). Surgical biopsy of the stalk showed Langerhans cell histiocytosis, which is only rarely isolated to the brain [13–18]. To date, there have been 16 reports of patients with unifocal brain involvement at the time of presentation. In 10 of these patients, the lesion involved the hypothalamus or posterior pituitary. In five of the 10 patients lesions subsequently developed at other sites of brain parenchyma [18]. Isolated involvement of the pituitary stalk generally is found in young women with diabetes insipidus.

The normal pituitary stalk enhances markedly with gadopentetate dimeglumine [11]. In our study, homogeneous enhancement of the pituitary stalk was noted after administration of gadopentetate dimeglumine in three patients (cases 1, 3, and 4). One patient (case 4) had an abnormally enhanced nodule in the hypothalamus that at surgery proved to be a greenish granuloma of Langerhans cell histiocytosis. While enhancement of the pituitary infundibulum with gadopentetate dimeglumine is normal, the pronounced enhancement of the thickened stalk in these patients was helpful.

The differential diagnosis of a thickened pituitary infundibulum includes germinoma, neurosarcoidosis, tuberculosis, infiltration from adjacent neoplasms (such as pituitary adenoma, hypothalamic glioma, or teratoma), and mass lesions adjacent to the infundibulum (such as craniopharyngioma, Rathke pouch cyst, tumors of the pituitary infundibulum, and metastasis). Patients with sarcoidosis and tuberculosis usually have abnormal chest films. Pineal germinomas usually enhance after IV administration of gadopentetate dimeglumine. They tend to infiltrate the pineal gland causing Parinaud syndrome (paralysis of upward gaze). Patients with primitive neuroectodermal tumors usually have symptoms related to the primary malignancy. Hematogenous metastases to the pituitary gland are most often encountered in older patients with lung or breast carcinoma. Pituitary adenoma or hypothalamic tumor with extension into the infundibulum are usually not associated with diabetes insipidus.

Three of our four patients had local radiation therapy. However, the diabetes insipidus remained unchanged. In one of these patients growth arrest and hypothyroidism developed. Greenberger et al. [19] reported reversal of diabetes insipidus in four of 21 irradiated patients with Langerhans cell histiocytosis. Three of the four patients who achieved a complete response were treated less than 1 week after the time of diagnosis. No spontaneous reversal of diabetes insipidus was observed in the series. Immediate radiation therapy may help prevent permanent damage to neuroendocrine cells. However, hypothalamic-pituitary dysfunction (i.e., growth hor-

mone deficiency and hypothyroidism) may follow local radiation [20–22]. Hypothalamic-pituitary dysfunction was noted in 25% of patients 5 years following initial local irradiation [20].

The dynamic changes in the size of the pituitary stalk are noteworthy. The stalks of three patients (cases 1–3) decreased in size after local radiation therapy. In one patient (case 1) the stalk enlarged again but regressed without further therapy. Diabetes insipidus persisted in all patients.

In summary, absence of the normal high-intensity signal of the posterior pituitary associated with a thickened pituitary stalk was found on MR in four female patients with diabetes insipidus. Two patients had associated abnormalities on either chest film or imaging studies of the temporal bone. Two patients had isolated Langerhans cell histiocytosis of the CNS. The MR appearance of a thickened stalk together with an absence of hyperintensity in the posterior pituitary, while perhaps nonspecific for Langerhans cell histiocytosis, should nonetheless prompt further studies, such as chest radiography, bone scanning, or temporal bone CT, in an effort to narrow the differential diagnosis. Further studies, both in normal patients and those with diabetes insipidus, are necessary to assess the specificity of this MR finding. Gadopentetate dimeglumine appears to be a useful adjunct in the MR examination of the patient with diabetes insipidus.

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