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Use of T1-Weighted MR Imaging to Differentiate between Primary Polydipsia and Central Diabetes Insipidus

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PURPOSE: To investigate the value of MR in differentiating patients with primary polydipsia, who have an intact neurohypophyseal system, from those with central diabetes insipidus, who have impaired synthesis and/or release of vasopressin. **METHODS:** Eighteen patients with clinically significant hypotonic polyuria were diagnosed endocrinologically as having primary polydipsia or diabetes insipidus (central or nephrogenic). These patients, and 92 patients without sellar disease, were then imaged with 1.5-T, T1-weighted, thin sagittal sections without gadolinium contrast. **RESULTS:** Normal hyperintense signal of the neurohypophysis was present in 90 of 92 patients without sellar disease. The signal was also present in all six patients with primary polydipsia. In contrast, the hyperintense signal was absent in all eight patients with central diabetes insipidus. Three of the four patients with nephrogenic diabetes insipidus also had an absent hyperintense signal. **CONCLUSION:** T1-weighted MR may prove important in differentiating patients with central diabetes insipidus from those with primary polydipsia.

Index terms: Diabetes insipidus; Sella turcica; Vasopressin

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The hyperintense signal (HIS) observed with T1-weighted MR of the normal posterior pituitary reflects an intact and functional neurohypophyseal system (1–3). The frequency of HIS in normal subjects varies among different investigators ranging from 52% (4), to over 87% (5), to as high as 100% in healthy volunteers (3, 6). The cause of HIS is disputed but is probably due to some constituent of the neurosecretory vesicles within the intact and functioning neurohypophysis (7). HIS is generally absent in patients with central diabetes insipidus (1, 8, 9). In addition, the signal is decreased in experimental animals that are chronically treated with hypertonic saline, presumably because arginine vasopressin (AVP) is depleted from the storage vesicles of the neurohypophysis (10).

Distinguishing primary polydipsia from central diabetes insipidus can be very difficult, especially when the latter is partial or incomplete. The basic pathophysiology of primary polydipsia and central diabetes insipidus differs in that in the former condition the release of AVP is inhibited by chronic overhydration and in the latter there is usually an intrinsic inability to synthesize AVP (see Discussion). In addition, animal studies demonstrate normal amounts of pituitary AVP in chronic hydration (11), and depletion of pituitary AVP in central diabetes insipidus (12). Consequently, we decided to investigate the potential value of magnetic resonance (MR) in differentiating between these two types of AVP-sensitive hypotonic polyuria.

Materials and Methods

Equipment

MR studies were done on high field strength (1.5 T) imaging equipment. Sagittal spin-echo midline images, 400-500/12-15 (TR/TE) were obtained with a 256 × 256 matrix, two signal acquisitions, and a field of view of 21–23 cm. The section thickness ranged from 3–5 mm with a 1-mm intersection gap.

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Patients

HIS is usually seen in the normal posterior pituitary gland on T1-weighted images through the sagittal midline of the brain. Because the frequency of this hyperintensity varies in the literature, we conducted a preliminary pilot study in 100 consecutive patients to determine the prevalence of HIS in a predominantly hospital-based population. Only patients who presented with non-sella–related symptoms, such as headaches, seizures, neurologic deficits, or following trauma were entered into the study. Included were two volunteers without any clinical symptoms. Patients who were found to have macroadenomas or empty sellae (5) and those with motion artifacts were excluded.

Eight studies met our exclusion criteria. Two of 92 cases had no appreciable HIS in the posterior pituitary. One was a 3-year-old boy with porencephaly. The other one was a 22-year-old woman with cerebral palsy. The preliminary study indicated an expected prevalence of HIS of approximately 98% in patients without macroadenoma or empty sellae. The absent HIS in the neurohypophysis was thus considered a relatively reliable indicator for hormonal dysfunction.

Eighteen adult patients were referred to us for clinically significant hypotonic polyuria (24-hour urine volumes of at least 3.6 liters). These patients were first evaluated by nonradiologic methods for the cause of their hypotonic polyuria, using well-established criteria (13–18). MR studies were subsequently conducted on the 18 patients after a clinical diagnosis of primary polydipsia, central diabetes insipidus, or nephrogenic diabetes insipidus had been made.

Image Analysis

The image with the best visualization of the posterior pituitary bright spot was selected for analysis. If HIS could not be separated from the fat marrow in the dorsum sellae, additional images were printed with a wider gray scale that facilitated the distinction between these two adjacent anatomic areas in all cases. Usually, the cortical margin of the dorsum sellae can be identified as a linear region of hypointensity. We assumed, that a bright signal posterior to this line represented the high signal intensity from fat marrow. If no distinction could be made or the linear low signal intensity of the cortical bone of the dorsum was in front of (anterior to) the clivus, the bright spot was considered absent. Image analysis was done by an experienced neuroradiologist, who was blinded to the nonradiologic diagnosis of the patients. Two cases were reviewed directly from the image screen of the viewer's console to confirm the absence of HIS.

Results

Prior to MR, the 18 patients were clearly diagnosed as having primary polydipsia, central diabetes insipidus or nephrogenic diabetes insipidus. Four patients who had hypotonic polyuria since birth were diagnosed as having nephrogenic diabetes insipidus because urine osmolality failed to increase following the injection of 5 U (12.5 μg) AVP, or 0.5 μg desmopressin (19). Eight patients were diagnosed as having central diabetes insipidus on the basis of having vasopressin-sensitive hypotonic polyuria with either markedly elevated or unattainable osmotic thresholds (Table 1). The osmotic threshold is the plasma osmolality when water-loaded patients begin to concentrate their urine during a hypertonic (5%) saline infusion. This represents the initial release of AVP. Therefore, the ability to release AVP in response to hypertonic saline was severely impaired in patients with central diabetes insipidus. In addition, all five of these patients who had water deprivation tests had markedly impaired urine osmolalities (Table 1). The cause of the central diabetes insipidus was idiopathic in five of the eight patients and the other three patients had specific causes listed in Table 1. Four patients were diagnosed as having primary polydipsia on the basis of normal osmotic threshold values (Table 1). Two other patients with AVP-sensitive hypotonic polyuria were also diagnosed as having primary polydipsia (Table 1). In one, a 45-year-old woman, the osmotic threshold was slightly elevated. However, other laboratory and clinical features, particularly the onset of symptoms when she was unable to eat solid food because of a severely damaged temporal mandibular joint, clearly establish the diagnosis (Table 1). The sixth patient diagnosed as having primary polydipsia, a 32-year-old woman, did not have an osmotic threshold study. However, she concentrated her urine well during water deprivation and she voluntarily stopped drinking excessively after counseling.

All patients with central diabetes insipidus but one, a 39-year-old man, were being treated with desmopressin at the time of imaging. Serum sodium levels at that time ranged from 131 to 149 mEq/L. The duration of symptoms at the time of imaging ranged from 3 months to 38 years. The six patients with primary polydipsia had symptoms from 2 months to 25 years and daily urine volumes ranged from 3.6 to 10.4 liters at the time of imaging. Their serum sodium levels ranged from 135 to 142 mEq/L at time of MR.

MR Results

Of the 92 patients without the sella-related disease who had MR as described, 90 had normal HIS emanating from the neural lobe of the pitui-

tary. The same was found in all six patients with primary polydipsia. In contrast, all eight patients with central diabetes insipidus were devoid of the signal. Of the four patients with congenital nephrogenic diabetes insipidus, HIS was present in one patient and absent in three.

TABLE 2: Occurrence of posterior pituitary hyperintense signal (HIS) in patients with hypotonic polyuria

	Vasopressin-Sensitive		Vasopressin-resistant: Congenital Nephrogenic Diabetes Insipidus
	Central Diabetes Insipidus	Primary Polydipsia	
HIS present	0	6	1
HIS absent	8	0	3

Discussion

This paper compares T1-weighted MR of the posterior pituitary in normal subjects, in patients with primary polydipsia, and in patients with central and nephrogenic diabetes insipidus. Ninety of 92 (98%) patients without sella-related disease studied by our technique were found to have the appropriate HIS. Eight patients with central diabetes insipidus were evaluated. These were males and females who had idiopathic diabetes insipidus or the lesions indicated in Table 1. The MRs were obtained anywhere from 3 months to 38 years following the onset of symptoms. At the time of MR, all but one patient, a 39-year-old man, were being treated with desmopressin, and serum sodium concentrations ranged from 131 to 149 mEq/L. HIS was absent in all eight patients (Table 2), and the absence was not due to the presumed compression of

TABLE 1: Characteristics of patients with vasopressin-sensitive hypotonic polyuria

Diagnosis	Cause of Disease	Duration of Disease at Time of MR	Age at Time of MR	Sex	Daily Urine Volume at Time of MR (liters)	Osmotic Threshold[a] (Normal = 285–292 mOsm/kg)	Maximum Urine Osmolality Attained during Water Deprivation Test (28) (Normal = 859 ± 260 (SD) mOsm/kg)	Other Observations That Support Diagnosis
Primary polydipsia		2 mo	21	M	6.0	287.7	500	
		2 mo	32	F	3.6	ND[b]	597	Variable random urine osmolality (183–732); symptoms stopped shortly after counseling
		1 yr	33	F	10.4	288.3	534	
		2½ yr	42	F	4.9	291.2	567	Taking psychoactive drugs which caused dry mouth
		25 yr	43	M	4.0	290.4	400	
		15 mo	45	F	5.4	294.1	682	Variable random urine osmolality (72–614); symptoms began when she fractured jaw and could not eat solid food
Central diabetes insipidus	Idiopathic	8 mo	36	F	12.0	>298	ND[b]	
	Idiopathic	38 yr	38	F	6.8	301.5	ND[b]	
	Idiopathic	3 mo	39	M	13.9	>298	110	
	Idiopathic	8 mo	40	F	8.5	>306	120	
	Idiopathic	5 mo	51	M	14.6	>310	107	
	Traumatic	11 yr	34	M	7.8	>324	108	
	Germinoma	4½ yr	35	M	10.8	>312	106	
	Suprasellar epidermoid cyst	5 yr	51	F	6.5	>313	ND[b]	

[a] Plasma osmolality at which antidiuresis begins in hydrated subjects being infused with 5% saline (13, 15).

[b] Not determined.

posterior lobe tissue which often occurs in patients with pituitary macroadenomas or empty sella syndrome even in the absence of diabetes insipidus (5). These observations strongly support the probability that the absence of HIS in these patients reflects the basic pathophysiologic abnormality of these patients with central diabetes insipidus, namely impaired synthesis, storage, and osmotically controlled release of AVP into the circulation. The one study conducted in man confirms the virtual absence of AVP in the posterior pituitary of a patient with central diabetes insipidus (20).

Even though none of our eight patients with central diabetes insipidus had HIS of the posterior pituitary, theoretically there are cases where it might be present. Occasional patients with central diabetes insipidus are apparently capable of synthesizing AVP but cannot release the hormone into the circulation in response to the usual osmotic stimulus. These patients may be capable of releasing AVP in response to nicotine, hypotension, nausea, and drugs such as chlorpropamide and clofibrate (21–24). They are considered to have osmoreceptor failure and have all of the usual clinical manifestations of diabetes insipidus. However, patients like these may be found to have HIS of the neurohypophysis.

All six patients with primary polydipsia had normal HIS emanating from the neural lobe of the pituitary (Table 2). This group was made up of both males and females, and, at the time of MR, were symptomatic for between 2 months and 25 years. They were all polyuric at the time of the MR study. The pathophysiologic implication of these studies is that patients with primary polydipsia have normal amounts of AVP in their neurohypophysis. No measurements of pituitary AVP content in patients with primary polydipsia are reported. However, mice with primary polydipsia have abundant neurosecretory material in the neurohypophysis (25), presumably reflecting adequate content of AVP. In addition, chronic overhydration of rats caused by the infusion of desmopressin and given liquid diets have normal amounts of AVP in their neural lobes (11).

The lack of HIS from the neural lobes in all eight of our patients with central diabetes insipidus and its presence in all six of our patients with primary polydipsia strongly supports the value of this observation in distinguishing between the AVP-sensitive hypotonic polyurias. This differential diagnosis may be extremely difficult, especially when the central diabetes insipidus is partial in nature. Urine osmolality can be low in relation to plasma osmolality in both conditions (13), and even the measurement of AVP by radioimmunoassay may not provide a definitive answer since the chronic overhydration in patients with primary polydipsia may lower AVP excretion and presumably synthesis and release in response to dehydration (14). The determination of the osmotic threshold for AVP by changes in free water clearance is perhaps the single best laboratory way of distinguishing between primary polydipsia and partial central diabetes insipidus (15). However, it is difficult to perform and many patients cannot tolerate the amount of 5% saline that must be infused. It is very important to properly distinguish between these two conditions because the approach to determining the underlying cause and the therapeutic options are different. For instance, antidiuretic therapy usually causes symptomatic hyponatremia if administered to patients with primary polydipsia.

Patients with nephrogenic diabetes insipidus have increased plasma and urine AVP (14, 18, 26), presumably in response to mild dehydration that occurs because of the difficulty in matching fluid intake to incessant severe water losses via the urine. Mice with congenital nephrogenic diabetes insipidus have normal or elevated stores of AVP in their neurohypophysis in comparison with normal mice (26, 27). This suggests that mice in a laboratory setting are successful in maintaining adequate hydration despite the presence of nephrogenic diabetes insipidus. There is no information on pituitary AVP content in patients with nephrogenic diabetes insipidus. However, our observations suggest that most of these patients are unable to maintain usual pituitary stores of AVP. This would be analogous to the loss of neurosecretory granules and presumed depletion of pituitary AVP in rabbits that are chronically treated with hypertonic saline (10).

In conclusion, appropriate T1-weighted MR revealed HIS of the neurohypophysis in 90 of 92 patients without sella-related disease. The signal was also present in all six patients with primary polydipsia. In contrast, HIS was absent in all eight patients with central diabetes insipidus. Since each disease was caused by a variety of factors and was present for varying durations with a range of serum sodium concentrations at the time of MR, it is reasonable to assume that in these AVP-sensitive polyuric patients, the MR reflected the expected normal content of neurohypophyseal AVP in patients with primary polydipsia, and

diminished AVP in patients with central diabetes insipidus. These observations should be very helpful in establishing the diagnosis between these two conditions. Three of four patients with AVP-resistant (nephrogenic) diabetes insipidus had absent HIS of the neural lobe. This probably reflects the state of chronic mild dehydration with subsequent depletion of pituitary AVP.

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Please see the Commentary by Kucharczyk on page 1293 in this issue.