Correlation between Magnetic Resonance Imaging of Posterior Pituitary and Neurohypophyseal Function in Children with Diabetes Insipidus

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ABSTRACT. The posterior pituitary lobe and stalk were studied by magnetic resonance imaging in 20 children with diabetes insipidus of different origins: primary familial autosomal dominant (n = 2) or idiopathic (n = 2), and secondary to craniopharyngioma (n = 6, resected in 5), to Langerhans cell histiocytosis (n = 5), to excessive water intake (dipsogenic; n = 3), to renal vasopressin insensitivity (n = 1), and to osmoreceptor dysfunction (n = 1).

Of the four children with primary diabetes insipidus, the posterior bright signal was recognizable in two with the familial autosomal dominant form and one with the idiopathic form; in the latter, the pituitary stalk was thin, while it was normal in the first two patients; no posterior hyperintense signal with enlarged and gadolinium-enhanced pituitary stalk was observed in the fourth. The posterior hyperintense signal was absent without evidence of ectopic posterior pituitary tissue regeneration in all five children with surgically removed craniopharyngioma and was doubtful in the child with unresented craniopharyngioma; the stalk was unrecognizable in all patients. In the five children with Langerhans cell histiocytosis, the posterior bright signal was absent, while the stalk was normal in two and unexpectedly enlarged in three (uniformly in two and mainly at the level of median eminence and hypothalamus in one). All five patients with dipsogenic or nephrogenic diabetes insipidus or osmoreceptor dysfunction had normal images of posterior pituitary lobe and stalk. Normal posterior pituitary bright signal and stalk were found in all 25 healthy control children.

Plasma vasopressin was undetectable in all patients except in nephrogenic one, in the child with osmoreceptor dysfunction, and in two of three dipsogenic children, the third mimicking partial neurogenic diabetes insipidus.

We conclude that 1) the absence of a magnetic resonance posterior pituitary signal in patients with central diabetes insipidus is always associated with hypothalamic-neurohypophyseal axis lesion; 2) the absence of the posterior pituitary bright signal correlates closely with undetectable plasma vasopressin only in the presence of organic hypothalamic-neurohypophyseal tract lesion; 3) evidence of posterior pituitary hyperintensity in diabetes insipidus patients does not necessarily indicate that functional integrity of the hypothalamic-neurohypophyseal axis is preserved; 4) the release of stored vasopressin may be impaired in some cases of autosomal dominant diabetes insipidus as well as in some idiopathic forms; and 5) evidence of isolated enlarged stalk in children with acute onset of diabetes insipidus suggests that magnetic resonance may disclose a preclinical-oligosymptomatic phase of systemic disorders (Langerhans cell histiocytosis dependent?) affecting the hypothalamic-neurohypophyseal tract. This could help to clarify both the natural history of anatomical and functional alteration during the course of diabetes insipidus and the origin of some idiopathic forms. Clear definition of isolated stalk alteration as a precocious manifestation of Langerhans cell histiocytosis could lead to early specific treatment in such patients. (J Clin Endocrinol Metab 74: 795-800, 1992)

CENTRAL nervous system dysfunction (DI) is a disorder characterized by chronic polyuria and polydipsia, corrected by vasopressin administration. It may be primary (idiopathic, sporadic, or familial) or, more often, acquired after injury to the hypothalamic-neurohypophyseal system (1, 2). Acquired DI is most frequently due to surgical removal of tumor in the hypothalamic-pituitary area. Organic lesion in this region may also be due to inflammatory diseases, such as Langerhans cell histiocytosis (LCH), sarcoidosis, tuberculosis, or autoimmune neurohypophysitis (1-6). Polydipsic conditions mimicking vasopressin (AVP) deficiency, such as dipsogenic DI and nephrogenic DI or the osmoreceptor dysfunction disease, are far less frequent (1, 3). The standard reliable way to diagnose central DI has been based on the AVP response to water deprivation, followed by administration of 1-desamino-8-D-arginine vasopressin (DDAVP), as well as by assessment of the renal response to hypertonic saline infusion.

Radiological computed tomography (CT) scan findings of neurohypophyseal system damage due to large lesions or, far less often, to small tumors of the pituitary stalk,
have been reported (7–11). Unfortunately, CT is not able to provide detailed and precise information on posterior pituitary abnormalities (12) or the hypothalamic-posterior pituitary axis function. Recently, magnetic resonance (MR) imaging proved able to identify normal posterior pituitary lobe by the characteristically hyperintense signal on T1-weighted image (12–15). This appears to be a hallmark of the functional integrity of the hypothalamic-neurohypophyseal tract (13, 14). Although the origin of the hyperintense signal of the posterior pituitary lobe is still a matter of discussion, the clear correlation between MR findings and hormonal and histochemical results seems to suggest the antidiuretic hormone contained in the neurosecretory granules (16, 17) and/or the intracellular lipid droplets in the pituicytes (18, 19) as its source. Although the absence of hyperintense signal in the posterior pituitary lobe is not diagnostic for central DI (20), hyperintensity is usually not observed in the course of DI (16, 21–26).

The aim of this study was to describe the MR imaging findings in our patients with DI of various etiologies, to assess the role of MR imaging in the diagnosis of DI, and finally, to explore whether the functional hypothalamic-neurohypophyseal defect has an anatomical basis.

**Subjects and Methods**

Twenty patients were enrolled in the study (12 males and 8 females, aged 14 months to 21 yr). Four of the 20 had primary central DI; 2 had familial autosomal dominant disease, and 2 were idiopathic. Of the other 16 children, 6 had histologically proven craniopharyngioma complicated by postoperative (in 5) or compressive (in 1) panhypopituitarism. Five children had histologically confirmed LCH, affecting bone and skin (4 of 5) or bone and liver (1 of 5); GH deficiency was present in 2, and TSH deficiency in 1. Three children had central dipsogenic DI diagnosed according to current criteria (1–3); 1 had nephrogenic DI, and 1 had hypothalamic osmoreceptor dysfunction. Fifteen of 20 were receiving treatment with DDAVP orally or intranasally; 1 received indomethacin-hydrochlorothiazide. The age range at the diagnosis of DI was 13 months to 12.7 yr. DI was assessed by the presence of urinary volume greater than 2000 mL/day, urinary osmolality measurement, water deprivation test, and DDAVP test (1–3).

**Water deprivation test**

A 6- to 7-h water deprivation test was carried out between 0830–1530 h and was stopped when weight loss exceeded 5% (27). In the five patients with postoperative DI, the test was not performed, as clinical features, basal serum sodium, and plasma osmolality as well as the DDAVP trial were diagnostic. Blood samples were drawn for measurement of serum sodium, osmolality, and AVP at the beginning and end of the test. Weight, urine volume, and osmolality were also recorded hourly.

**DDAVP test**

DDAVP (10–25 μg, twice a day) was given intranasally. The urinary volume was monitored during free intake of fluids and food during 2–3 days before and 2 days after the beginning of the DDAVP test. Urinary and plasma osmolalities were measured every 1–2 h during the first 8 h. Plasma and urinary osmolalities were measured as freezing point depression by Advanced Osmometer Knauer Type M, Adenauerallee, Germany. Plasma AVP was measured by a RIA technique (Medica Systems, Genova, Italy) (28).

**MR study**

MR imaging was performed by 0.5 T (2 cases) and 1.5 T units, using spin-echo T1-weighted images (TR, 400 ms; TE, 15 ms; 4 acquisitions). Sagittal and coronal 3-mm sections with full matrix size of 256 × 256 pixels and a field of view of about 20 cm were obtained. T1-weighted images were obtained after intravenous administration of gadolinium-diethylenetriamine-pentaacetic acid (Gd-DTPA) administration (0.2 mL/kg) in 1 patient (case 4). MR imaging of the posterior pituitary lobe and stalk was performed on 20 control children (age range, 8–15 yr) without evidence of polyuria and polydipsia, who were being investigated because of short stature.

**Results**

At the time of diagnosis, plasma osmolality above 295 mosmol/kg and sodium concentration above 143 meq/L under basal conditions of ad libitum fluid intake were found in the five patients with craniopharyngioma after surgery. Low serum sodium levels with plasma and urinary hyposmolality were present in two patients with dipsogenic DI. Chronic hyposalinemia (range, 298–315 mosmol/kg) and hypernatremia (range, 148–157 meq/L) with hypodipsia and recurrent fever led to the diagnosis of hypothalamic osmoreceptor dysfunction in case 20.

**Water deprivation test**

Fourteen of 20 patients were examined. Increased serum sodium and plasma osmolality with lack of increase in urinary osmolality were obtained after 7 h in 4 of 4 patients with primary DI and 6 of 15 (1 of 6 craniopharyngioma; 5 of 5 LCH) patients with secondary DI. In 1 dipsogenic DI patient, the response to the deprivation test was similar to that of the partial nephrogenic DI patients; 2 of 3 had mild increase in serum sodium and plasma and urinary osmolalities. The level of plasma AVP is shown in Table 1.

**DDAVP test**

Sixteen of 20 patients showed reduction of water intake and urine volume with increased urinary osmolality. Dilutional hyponatremia and hyposmolality developed with persistent water intake in the 3 dipsogenic patients.
One of these patients (case 16) developed hypotonic seizures (29). Diluted urine excretion after DDAVP was observed in case 19.

**MR study**

A bright signal recognizable as the posterior pituitary lobe was detected in 2 autosomal dominant and 1 idiopathic DI patient (cases 1–3). The stalk was normal in cases 1 and 2 and thin in case 3 (Fig. 1). In case 4, the hyperintense signal was absent, and the stalk was uniformly enlarged, with positive Gd-DTPA enhancement (Fig. 2). The hyperintense signal was undetectable in 5 patients with craniopharyngioma (cases 5–9) and was doubtful in 1 (case 10) due to intrasellar fat and pad and fatty marrow of the dorsum sellae. The stalk was unrecognizable in all patients (cases 5–10; Fig. 3). No ectopic bright signal in the hypothalamus was identified. The posterior signal was not detected in the pituitary fossa in any of the five patients with LCH. The stalk was enlarged in 3 (cases 13–15), uniformly in 2 (cases 13 and 14) and mainly at the level of median eminence and hypothalamus in 1 (case 15); it was normal in 2 (cases 11 and 12; Fig. 4). Normal images of pituitary stalk and posterior pituitary lobe were observed in the 3 dipsogenic patients, the nephrogenic patient, the subject with osmoreceptor dysfunction, and the 25 controls.

**Discussion**

The role of MR in the differentiation of DI is not yet completely defined. The posterior pituitary bright signal, initially thought to be due to fat within the sella turcica (13), was also attributed to the AVP content in the neurosecretory granules (16–18) and/or intracellular lipid droplets in the glial cell pituicytes of the posterior lobe (19). The signal, reported in 90–100% of normal
subjects (20, 24, 30) as well as in all of our controls, appears to be closely related to normal hypothalamic-neurohypophyseal axis function. Moreover, its volume reflects the hormonal release function from the neurohypophysis (18). Although its absence is not diagnostic for central DI, hyperintensity is not usually observed in central DI. Only two idiopathic DI patients (whose plasma AVP levels were not reported) (25), one dipso-
genic and one with hypothalamic osmoreceptor dysfunc-
tion (31), have been reported as having normal posterior hyperintense signal. This could be attributed to the specific alterations, not involving AVP synthesis.

The basic defect underlying autosomal dominant DI is still unclear. A familial tendency toward dysgenesis or degeneration of the supraoptic-paraventricular nucleus has been suggested on the basis of autopsy findings (32-34). Recently, molecular analysis suggested that a defective AVP-preprovasopressin-neurophysin-II-glycoprotein gene (35, 36) may result in autosomal dominant DI (37). Autosomal recessive DI in rats resulted from a single nucleotide deletion in the neurophysin gene (38). Two of our children with autosomal dominant DI unexpectedly had a normal bright signal, no hypothalamic lesion, and an undetectable plasma AVP (39). This suggests that, at least in some cases, children with autosomal dominant DI are able to synthesize and store some amount of AVP in the posterior pituitary, but not necessarily to release it normally. In one recent report, five members of one family with autosomal dominant DI had either preserved or absent posterior bright signal (40).

The term idiopathic DI describes a group of patients with chronic polyuria, polydipsia, and AVP deficiency in the absence of any alteration that is known to be responsible for DI. The present cases 3 and 4 fulfill current criteria for this diagnosis. Nevertheless, in one case while plasma AVP was undetectable, a posterior pituitary signal was evident. This is apparently in agreement with the observation made by Cacciari et al. (25) in two idiopathic DI patients, but is in contrast with the report of absent hyperintense signal in eight children with idiopathic DI (24), suggesting heterogeneity of the group of patients with idiopathic DI. This is also supported by recent evidence of two cases of idiopathic DI, as the presentation of germinoma that became evident only 6 and 21 yr later (41). Impairment of AVP release, as here hypothesized for the autosomal dominant DI, could not be excluded. One would expect AVP synthesis to be
associated with neurophysin production. Nevertheless, at least one exception was reported (42). This defect might explain the presence of the posterior pituitary hyperintense signal despite undetectable plasma AVP in the course of DI. In such cases, proteolytic degradation could impair normal secretion (38).

In the other case of idiopathic DI with undetectable plasma AVP, posterior signal was absent, and the stalk was uniformly thickened. The differential diagnosis of thickened pituitary stalk includes germinoma, neurosarcoïdosis, tuberculosis, infiltration from mass lesion, adjacent neoplasm, or distant metastasis (43). Our patient had no signs of sarcoidosis or tuberculosis, and no visible mass or other primary tumor, while this subject resembled three of our five children with LCH. Some recent reports suggest that patients with central DI and either localized or systemic LCH have a combination of thickened pituitary stalk and absence of hyperintense signal (21, 23, 26). Moreover, this picture is reported in some cases of DI of unknown origin (23, 26). As isolated central nervous system involvement in LCH is well documented (21, 23, 26, 44-47), we suppose that the picture of uniformly thickened stalk observed in the present case 4 in the absence of any other clinical and laboratory finding is highly suggestive of stalk involvement of isolated LCH.

We considered the risk/benefit balance of histologically proven diagnosis of LCH not to favor such an aggressive procedure in this case. Follow-up of the patient will clarify whether this is an isolated or a preclinical stage of systemic LCH which became evident 4 yr after isolated histologically proven, LCH-dependent stalk enlargement in one case (48).

The hyperintense signal was absent in all children with overt LCH, in agreement with previous reports (16, 21-23, 26), while the stalk was normal in two and enlarged in three. Preliminary evidence of possible normalization of formerly thickened stalk (21) could suggest that these variations may represent different states of activation of the localized inflammatory process underlying LCH.

Our children with resected craniopharyngioma had persistent DI and undetectable posterior signal (17, 20) and no evidence of ectopic posterior pituitary tissue regeneration within the hypothalamus, as suggested by El Gamal et al. (49). One patient with unresected craniopharyngioma also lacked posterior hyperintensity, probably because of tumor compression of the pituitary. In the presence of intrasellar mass, displacement of the neurosecretory material transported from the hypothalamus to neurohypophysis with accumulation proximally to the obstruction has been demonstrated (20). We suggest that surgical stalk transection or tumor compression of the pituitary gland is responsible for ischemic lesions of the pituitary, leading to panhypopituitarism and DI, without evidence of dislocation or tissue regeneration of the neurohypophysis. The relationship between undetectable circulating AVP and the absence of posterior signal in central DI seems to be confined to cases of DI due to hypothalamic-neurohypophyseal lesion, as in LCH and craniopharyngioma.

Dipsogenic DI is rare in children and is occasionally difficult to differentiate from the neurogenic form (3). Normal plasma AVP levels with normal bright signals were observed in our cases 17 and 18, while in case 16, overhydration suppressed AVP release, mimicking the AVP deficiency. After correction of water intake, the AVP defect was reversed. In this child, posterior signal was present at diagnosis, even with undetectable plasma AVP. This suggests that the bright signal is associated with storage of normally or at least partially synthesized AVP, even if inadequately released. The patient with nephrogenic DI had a normal MR image and high normal plasma AVP levels, as would be expected since AVP synthesis is not impaired. There is no previous report available on MR imaging in such patients. The child with osmoreceptor dysfunction showed detectable plasma AVP and posterior signal, as in the only reported case (31).

We concluded that the absence of a MR posterior pituitary signal in patients with DI is always associated with hypothalamic-neurohypophyseal axis lesion and correlates closely with undetectable plasma AVP. On the contrary, evidence of posterior pituitary hyperintensity does not rule out diagnosis of central DI, as release of stored AVP may be impaired in some cases of autosomal dominant DI as well as in some idiopathic forms. Isolated enlarged stalk in children with acute onset of DI suggests that MR may be useful for the recognition of a preclinical phase of systemic disorders (LCH dependent?) affecting the hypothalamic-neurohypophyseal tract. This could help to clarify both the natural history of anatomical and functional alterations in the course of DI and the origin of some cases of idiopathic DI. MR evaluation in the follow-up of patients with idiopathic DI could help to improve our knowledge of this unclear condition, while the clear definition of stalk alteration as a precocious manifestation of LCH could provide noninvasive diagnosis and lead to early specific treatment in such patients.

References
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