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Persistent High MR Signal of the Posterior Pituitary Gland in Central Diabetes Insipidus

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Summary: We describe three cases of central diabetes insipidus, each with a different pathogenesis, in which unexpected hyperintensity of the posterior pituitary gland was seen on T1-weighted MR images obtained at the time of presentation. In the first case (idiopathic), the posterior pituitary signal persisted more than 10 years; in the second case (Langerhans cell histiocytosis), the signal disappeared within 3 months, despite early specific chemotherapy with etoposide; and in the third case (transient), the posterior signal disappeared within 1 year, but it was documented at the time of spontaneous reversal of polyuria and polydipsia.

Index terms: Diabetes insipidus; Histiocytosis; Pituitary gland, magnetic resonance

Central diabetes insipidus is a heterogeneous condition characterized by polyuria and polydipsia due to arginine vasopressin (AVP) deficiency. Acquired central diabetes insipidus may be due to hypothalamic–pituitary stalk lesions that occur in the course of inflammatory disorders, such as Langerhans cell histiocytosis (LCH) (1, 2) or idiopathic granulomatosis (3), or to a neoplastic process, such as germinoma (4). In 30% to 50% of cases it is idiopathic (5). Rarely, diabetes insipidus is familial, with autosomal dominant inheritance (6).

The clinical and biochemical diagnosis of diabetes insipidus is supported by the absence of the posterior pituitary bright signal on magnetic resonance (MR) images (7). In fact, hyperintensity of the posterior pituitary usually, but not invariably, accompanies hypothalamic–posterior pituitary functional integrity, as observed in healthy control subjects and in patients with primary polyuria or nephrogenic diabetes insipidus (3, 8, 9). The absence of a posterior pituitary hyperintensity in a patient with central diabetes insipidus can be the only and earliest evidence of hypothalamic-pituitary neoplasm (10). Our group (3) and Miyamoto et al (11) have previously described the persistence of the posterior pituitary signal in autosomal dominant central diabetes insipidus. Sporadic cases were included in two other reports of patients with multiple pituitary hormone deficiency (12) or LCH (13); however, the issue was not specifically addressed and no follow-up was provided.

We describe three patients with central diabetes insipidus, two permanent and one transient, in whom MR imaging was performed at the time of diagnosis and at follow-up. In all patients a posterior pituitary signal was present at the time of diagnosis. In one case it persisted more than 10 years after onset, while in one it disappeared within 3 months. In the third patient, with transient diabetes insipidus, the signal was present initially, then disappeared, and finally became evident concurrently with clinical normalization.

Case Reports

Case 1

A boy was first seen at 21 months of age because of polyuria and polydipsia, which had persisted for 8 months. The water-deprivation test and 1-desamino-8-D-arginine vasopressin (DDAVP) trial were compatible with central diabetes insipidus. The plasma level of AVP was less than 1 pg/mL after the dehydration test (normal, 2 to 6 pg/mL) (2). Intranasal DDAVP treatment was successful. Thyroid hormone levels were normal and growth was at the 75th percentile for age. MR imaging performed at 5 years of age showed a normal posterior pituitary signal on T1-weighted images, normal morphology of the anterior gland, and a thin stalk. Repeat MR imaging at the ages of 8, 9, and 11 years revealed unchanged anterior pituitary gland and stalk morphology with a persistence of the posterior pituitary signal (Fig 1). DNA analysis performed according

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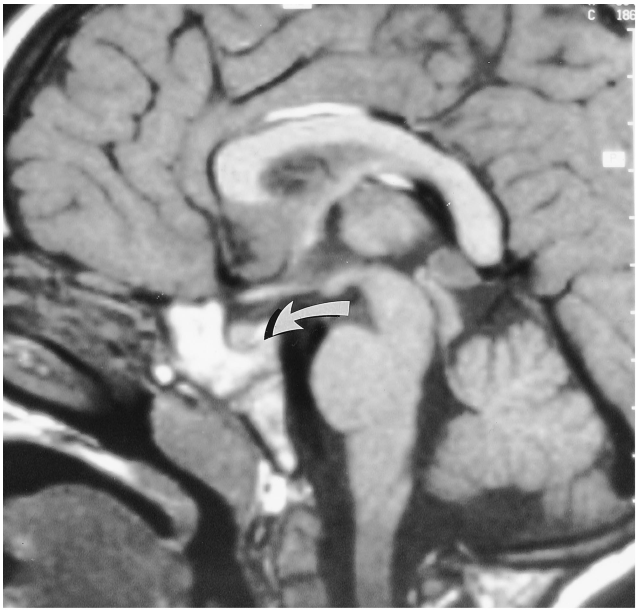
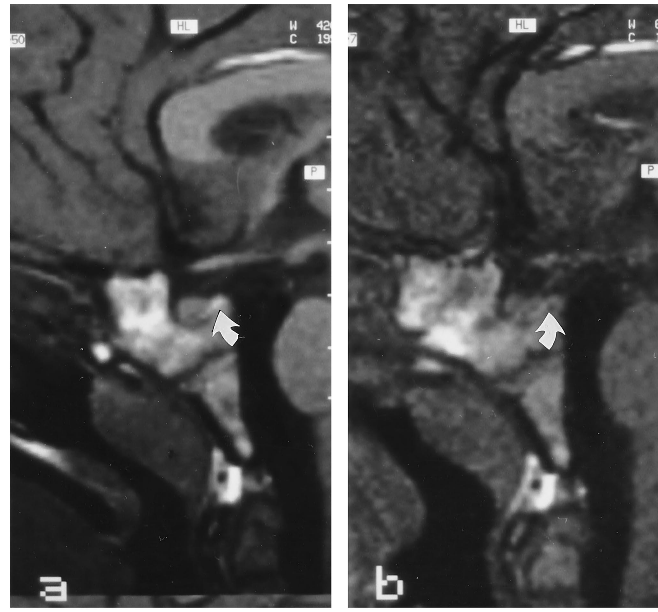


Fig 1. Case 1: Idiopathic isolated central diabetes insipidus in 11-year-old boy. Sagittal T1-weighted MR image (300/15/3 [repetition time/echo time/excitations]; section thickness, 3 mm; matrix, 256 × 256) shows posterior pituitary hyperintensity (*arrow*) and normal morphology of anterior pituitary and stalk.



A B

Fig 2. Case 2, Langerhans cell histiocytosis with associated central diabetes insipidus in 3-year-old boy.

A, Sagittal T1-weighted MR image (300/15/3; section thickness, 3 mm; matrix, 256 × 256) at disease onset shows posterior pituitary hyperintensity (*arrow*) and normal morphology of anterior pituitary and stalk at onset.

B, Sagittal T1-weighted MR image (350/15/2) after 2 months shows disappearance of posterior pituitary signal (*arrow*).

to Repaske et al (6) excluded AVP neurophysin-II gene mutation.

Case 2

A boy was first seen at 4 months of age because of otitis and skin rash. LCH was diagnosed from a biopsy sample. Treatment was started with vinblastine and steroids (14). At 2 years 9 months of age, the disease reactivated with bone lesions, which were treated with local steroid injection. At 3 years 4 months of age, additional bone lesions and diabetes insipidus developed. MR images showed normal brain, including the hypothalamic pituitary region. The posterior pituitary signal was dim. Etoposide rescue chemotherapy was started immediately, together with intranasal DDAVP. Within 3 months, the posterior pituitary signal had disappeared (Fig 2). One year later, the child was doing well and was off therapy.

Case 3

A girl had her menarche at 12 years, and galactorrhea began at 13 years 10 months of age, followed by amenorrhea. She was first seen at another hospital at 15 years of age because of polyuria and polydipsia (6 to 8 L/d). Basal urine osmolality was 101 mOsm/kg and it was 442 mOsm/kg after 20 hours of water deprivation (normal, >700 mOsm/kg). These results were compatible with central diabetes insipidus. DDAVP trial was followed by normalization of water intake and output. The plasma level of AVP was <1 pg/mL after the dehydration test (normal, 2.5 to 5 pg/mL). DDAVP treatment was successful, and regular menses followed treatment with ethinylestradiol and progesterone. MR imaging performed at another hospital showed normal posterior pituitary signal and normal morphology of anterior pituitary gland and stalk on T1-weighted images. One year later, the anterior pituitary and stalk morphology was unchanged, and the posterior pituitary signal had disappeared. At 16 years 16 months after the onset of central diabetes insipidus, and while she was on DDAVP therapy, the patient experienced spontaneous excessive water retention and reduced water intake. DDAVP therapy was withdrawn and a water deprivation test was performed. Basal urine osmolality was 593 mOsm/kg and 969 mOsm/kg after 12 hours of water deprivation. These data were not compatible with persistent central diabetes insipidus. MR imaging revealed unchanged anterior pituitary gland and stalk morphology, while the posterior pituitary signal became evident.

Discussion

MR findings in central diabetes insipidus are characterized by a lack of high signal intensity of the posterior pituitary on T1-weighted images, which is often associated with a hypothalamic–pituitary stalk lesion (2, 7). Persistent hyperintensity of the posterior pituitary has been described primarily in patients with familial autosomal dominant central diabetes insipidus (3, 11) and, rarely, in patients with idiopathic (3, 12) or lesional (13) central diabetes insipidus.

Appearance of the posterior pituitary signal has been ascribed to fat within the sella, to lipid accumulation within the pituicytes, or to the secretory granules containing AVP. Yet, posterior pituitary signal closely correlates with the functional status of the posterior pituitary gland (9). Persistence of the posterior pituitary signal despite the absence of plasma AVP in patients with autosomal familial central diabetes insipidus may be explained by the molecular mechanism of AVP synthesis (15). Impaired AVP neurophysin-II tetramerization, resulting from a mutated protein or accumulation of abnormal precursor molecules within the hypothalamic cells, could lead to a progressive retrograde toxic degeneration of the AVP neurophysin-II neurons, which could be responsible for the disappearance of the posterior pituitary signal (11). This hypothesis is compatible with the natural history of the autosomal dominant form of central diabetes insipidus, in which the AVP defect may develop with time (16), and it explains the pathologic finding of a reduced number of AVP-producing cells at brain autopsy (17). In our patient with early-onset central diabetes insipidus and persistent posterior pituitary signal, DNA sequencing excluded AVP neurophysin-II gene mutation. Although disruption of mRNA processing by a different mutation could be hypothesized, this is not demonstrable. Thus, idiopathic central diabetes insipidus with persistent pituitary signal may occur in patients who lack associated conditions at more than 10 years' follow-up.

Our case 2 provides evidence that the posterior pituitary signal may be present at the time lesional central diabetes insipidus is diagnosed. Because symptomatic central diabetes insipidus may occur after the destruction of 90% of the hypothalamic nuclei, the residual tissue might explain the persistence of the posterior pituitary signal at the time of diagnosis. Complete destruction of the nuclei may be followed by disappearance of the posterior pituitary signal, which, in our patient, occurred within 3 months. It is possible that prompt MR imaging of patients at the onset of lesional central diabetes insipidus may reveal that this occurrence is more common than we realize.

The pathogenesis and clinical course of disease in our patient in case 3, who had galactorrhea followed by secondary amenorrhea due to hypogonadotropic hypogonadism and transient central diabetes insipidus, remain unclear. Transient central diabetes insipidus has been described after head surgery or severe brain trauma with skull fracture (18), but these were not present in this patient. On the other hand, the long-term water deprivation test at the time of diagnosis and the normalization of water homeostasis during DDAVP treatment excluded primary polydipsia. Furthermore, the persistence of hypogonadotropic hypogonadism also favored occult hypothalamic involvement, as suggested by normal MR findings.

Combined or multiple pituitary hormone deficiency has been described in association with MR imaging alterations; that is, lack of posterior pituitary signal with or without pituitary stalk involvement. Unexpectedly, neither the pituitary stalk nor the posterior signal was affected in this case. Although the persistence of the posterior pituitary signal at the time of diagnosis of central diabetes insipidus may have been due to subtotal depletion of hypothalamic AVP secretory neurons, the subsequent disappearance and reappearance of posterior pituitary signal at follow-up require further elucidation.

The absence of posterior pituitary signal has been reported in as many as 48% of healthy subjects, regardless of age (19). This issue remains controversial, as age standards are not available, and decline in kidney function, including ability to concentrate the urine, reduces posterior pituitary AVP content. This may account for changes in MR signal. In our experience with over 100 children with normal water homeostasis who underwent single or repeated MR imaging, we never observed disappearance of the posterior pituitary bright signal (data not shown). Moreover, it is unlikely that day-to-day variations of water balance play a role in the posterior pituitary AVP store, which is usually stable over 1 week to 1 month, owing to the long half-life of mRNA (20). This is consistent with the observation that in animals hypertonic saline infusion over 2 weeks leads to marked but not complete depletion of neurosecretory granules and to a decrease (but not disappearance) of posterior pituitary signal (21). Thus, disappearance of the posterior pituitary signal in our patient is suggestive of deficient AVP synthesis, while its reappearance may be considered evidence of functional rescue.

In conclusion, persistence of the posterior pituitary bright signal can be documented early in central diabetes insipidus, indicating that a single MR imaging examination at the onset of disease might not be sensitive in these patients. Most patients will lose their posterior pituitary signal, but occasionally some do not. In patients with LCH-dependent central diabetes insipidus, specific etoposide chemotherapy given immediately after clinical onset of the disease might not be effective in reversing its clinical features or in preventing the disappearance of the posterior pituitary signal.

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