Central Diabetes Insipidus Resulting from a Nonneoplastic Tiny Mass Lesion Localized in the Neurohypophysyal System

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With the advent of magnetic resonance imaging (MRI), the neurohypophysyal system can be clearly delineated and its functional integrity can be predicted. The authors describe seven cases of central diabetes insipidus (DI) that occurred spontaneously. MRI revealed that the normal hyperintensity of the pituitary posterior lobe, which has been thought to be the neurosecretory material containing antidiuretic hormone, was absent in all cases. In addition, enlargement of a part of the neurohypophysyal system was recognized in five of seven cases on MRI. Three of the five patients with enlargement of a part of the neurohypophysyal tract underwent biopsy and were demonstrated to have chronic inflammation of the neurohypophysyal system. It was demonstrated that the enlarged parts of the neurohypophysyal system had shrunk either spontaneously or after the biopsy in four of the five cases. All patients are alive and have not experienced progression or remission of the disease. This study indicates that some cases of idiopathic DI result from a tiny mass lesion, usually nonneoplastic, localized in the neurohypophysyal system.

KEY WORDS: Diabetes insipidus; Magnetic resonance imaging; Pituitary stalk; Chronic inflammation

Diabetes insipidus (DI) is a syndrome characterized by polyuria and polydipsia; in the central form symptoms are due to a deficiency of circulating antidiuretic hormone. Many disorders affecting the neurohypophysyal system may lead to central DI. However, idiopathic cases constitute the major group of central DI [2,8]. Actually, most of the spontaneously acquired cases are diagnosed as idiopathic DI [20]. In this regard, one can postulate that perhaps only the lack of reliable methods of investigation of pituitary–hypothalamic diseases is responsible for this fact. Magnetic resonance imaging (MRI) clearly delineates the hypothalamus, the pituitary stalk, and the pituitary gland [5]. In addition, MRI can predict DI specifically [3,6]. We recently had the opportunity to investigate by MRI seven patients suffering from spontaneously acquired DI. MRI has revealed that most patients with central DI have some kind of abnormality in the pituitary posterior lobe and/or pituitary stalk.

Several cases of central DI caused by a small mass lesion localized in the pituitary posterior lobe and/or pituitary stalk have been reported in the literature. They were histiocytosis X [7,14,15,17,18,22], sarcoidosis [12,17], Erdheim–Chester’s disease [21], and germinoma [1,16]. In this study, three patients underwent biopsy. We provide histological as well as MR findings and then discuss the clinical features and etiology of spontaneously acquired cases of central DI.

Summary of Cases
Subjects
Between 1987 and 1990, seven patients with central DI were evaluated at Kyoto University Hospital (Table 1). The symptoms of DI were spontaneously acquired in all seven cases. Three patients were male and four were female, ranging in age of onset from 3 to 56 years (average 29.6 years).

Clinical Features
All seven patients had had a sudden and spontaneous onset of the symptoms: polyuria and polydipsia. The diagnosis of central DI was established endocrinologically. All patients except a 28-year-old woman (case 7) were diagnosed as having complete DI. All patients were treated with intranasal vasopressin to which they responded well, and no patient has experienced remission of the symptoms.

Endocrinological evaluation revealed that in all patients but the woman with partial DI (case 7) the response of growth hormone (GH) to arginine- or insulin-induced hypoglycemia was poor. This poor response of
Table 1. Clinical Summary of Seven Patients with Central Diabetes Insipidus

<table>
<thead>
<tr>
<th>No.</th>
<th>Age/sex</th>
<th>Symptom(s)</th>
<th>Hormonal abnormality</th>
<th>Findings of MRI</th>
<th>Histology</th>
<th>Follow-up result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>6/6/M</td>
<td>Acute DI</td>
<td>Low GH secretion</td>
<td>Enlarged</td>
<td>Loss of high intensity on T₁-WI</td>
<td>Chronic inflammation</td>
</tr>
<tr>
<td>2.</td>
<td>18/11/M</td>
<td>Acute DI</td>
<td>Panhypopituitarism</td>
<td>Enlarged</td>
<td>Loss of high intensity on T₁-WI</td>
<td>ND</td>
</tr>
<tr>
<td>3.</td>
<td>48/48/F</td>
<td>Acute DI</td>
<td>Low GH secretion</td>
<td>Enlarged</td>
<td>Loss of high intensity on T₁-WI</td>
<td>Chronic inflammation</td>
</tr>
<tr>
<td>4.</td>
<td>3/3/F</td>
<td>Acute DI</td>
<td>Low GH secretion</td>
<td>Enlarged</td>
<td>Loss of high intensity on T₁-WI</td>
<td>ND</td>
</tr>
<tr>
<td>5.</td>
<td>55/55/M</td>
<td>Acute DI</td>
<td>Low GH secretion</td>
<td>Not enlarged</td>
<td>Enlarged; loss of high intensity on T₁-WI</td>
<td>Chronic inflammation</td>
</tr>
<tr>
<td>6.</td>
<td>66/56/F</td>
<td>Acute DI</td>
<td>Low GH secretion</td>
<td>Absent</td>
<td>Loss of high intensity on T₁-WI</td>
<td>ND</td>
</tr>
<tr>
<td>7.</td>
<td>28/28/F</td>
<td>Acute DI (partial)</td>
<td>Low GH secretion</td>
<td>Not enlarged</td>
<td>Loss of high intensity on T₁-WI</td>
<td>ND</td>
</tr>
</tbody>
</table>

* Age at the time of evaluation.
* ND, not determined.

GH did not need to be compensated in any of the patients except for an 18-year-old boy who had panhypopituitarism (case 2).

None of these patients showed signs or symptoms other than those caused by pituitary dysfunction. Routine roentgenographic study including skull and chest X-ray films revealed no abnormality in any of the cases. Routine computed tomographic (CT) scans of the brain showed no apparent abnormal mass in any of them.

**MRI Findings**

All patients underwent MRI of the pituitary–hypothalamic region. MRI was performed on a 1.5-T superconductive imager (Signa, GE). Images were obtained with a head coil with 24 cm of field of view, a 256 × 256 data matrix, 3- or 5-mm slice thickness, and 2 or 4 of averages. The T1-weighted images were obtained by partial saturation technique with a repetition time (TR) of 400 ms and an echo time (TE) of 25 ms.

MRI revealed loss of high intensity in the posterior lobe in all patients on T1-weighted images. The posterior lobe had the same intensity as the pituitary stalk and anterior lobe on T1-weighted images.

In four of the seven patients (cases 1–4) the pituitary stalk was enlarged (Figures 1, 2, 5). The enlargement was maximal just below the median eminence and minimal just above the pituitary gland in the four cases. Gadolinium diethylene-triamine-pentaacetic acid (DTPA) brightly enhances the enlarged pituitary stalk and the pituitary gland all together (Figure 2). In one patient, a 55-year-old man (case 5), the posterior lobe was enlarged although the pituitary stalk seemed to be normal (Figure 3, left). In another patient, a 66-year-old woman (case 6) who underwent MRI 10 years after the onset of the symptoms, the pituitary stalk seemed to have disappeared (Figure 3, right). In the patient with partial DI (case 7) no abnormality was noted except for loss of the high intensity in the posterior lobe on a T1-weighted image.

**Histological Findings**

Three of the seven patients underwent biopsy. In a 6-year-old boy (case 1) and a 48-year-old woman (case 3), whose pituitary stalks were enlarged on MRI, biopsy was performed following the right ptorial approach. In these cases the pituitary stalk was enlarged and had a grayish appearance under the operative microscope. In a 55-year-old man (case 5) whose posterior lobe was enlarged, biopsy was done by the transsphenoidal approach. All the surgical specimens obtained from the three patients showed only infiltration of lymphocytes and plasma cells into the pituitary stalk and posterior lobe (Figure 4). The histological diagnosis was non-specific chronic inflammation.

**Clinical Course**

All patients are alive and are leading a fairly normal life while using intranasal vasopressin. In all three patients...
who underwent biopsy, shrinkage of the enlarged pituitary stalk or posterior gland was observed. No recurrence has been recognized during the follow-up period in these cases. In one patient, for whom the histology of the lesion was unknown, spontaneous shrinkage of the enlarged pituitary stalk was recognized (Figure 5).

Discussion

MRI Findings

In all seven patients with central DI, the normal hyperintensity of the posterior pituitary lobe was absent on the sagittal T1-weighted image. It has been reported that all patients with central DI lose the hypersignal in the posterior pituitary gland [3,6,9,10,22]. Fujisawa et al [6] speculated that the hypersignal may be due to the neurosecretory material in the axons of the hypothalamohypophyseal tract. Our results support this speculation. MRI indicates functional integrity of the neurohypophyseal system and is important in diagnosing DI.

Pathogenesis of Central DI

Ischemic lesions, hemorrhage, trauma, infection, histiocytosis X, sarcoidosis, and intracranial tumors—includ-
ing germinomas and optic and hypothalamic gliomas—may lead to central DI [19]. However, the causative factor in 30%–50% of the cases remains unknown [8]. Some cases are of familial DI and the onset of symptoms takes place soon after birth [11], but idiopathic DI is usually sporadic and spontaneously acquired at any age. Characteristically, the onset of the symptoms is abrupt, and prognosis of patients with idiopathic DI is reportedly good [4,8]. Our seven cases could be categorized into idiopathic DI without an MRI or CT of high quality. There are few published observations about the appearance of the neurohypophyseal system on MRI or CT in patients with idiopathic DI. Manelfe and Louvet [13] reported that 8 of 12 cases with central DI had several modifications in the neurohypophyseal system on CT. On the other hand, Gudinchet et al [9] reported that eight patients with primary DI showed normal anatomy of the hypothalamic and pituitary region on MRI, although they were not certain about whether these cases were idiopathic or familial. In our series, the MRI showed an enlargement of a part of the neurohypophyseal system in five of the seven cases. In these cases DI

Figure 3. T1-weighted magnetic resonance images show enlargement of the posterior pituitary lobe (left) in a 55-year-old man (case 3) and absence of the pituitary stalk (right) in a 60-year-old woman (case 6).

Figure 4. Photomicrographs of the surgical specimens, showing chronic inflammation localized in the pituitary stalk (A, B) or the pituitary posterior lobe (C). (A) Case 1; (B) Case 3; (C) Case 5 (hematoxylin and eosin; bar: 30 μm).
was thought to be due to a small mass lesion localized to the neurohypophyseal system. According to Czernichow et al [4], anterior pituitary dysfunction is frequently noted in patients with idiopathic DI. He has indicated that the causative factor of idiopathic DI may not be a degenerative process in the vasopressin-synthesizing cells, but it may be a mass lesion that can affect the adenohypophysial system. In our study all cases that had enlargement of the neurohypophyseal system on MRI had poor GH secretion after arginine- or insulin-induced hypoglycemia. This fact fits well the theory that some cases of idiopathic DI result from tiny mass lesions in the neurohypophyseal system.

Histology of the Tiny Mass Lesions
The tiny mass lesion that causes central DI is usually neoplastic, and the prognosis of patients with idiopathic DI is reportedly good, as in our cases. Although germinomas localized in the posterior pituitary lobe [1,16] and in the pituitary stalk [9] have been reported, these may be rare because germinomas rapidly grow into the optic chiasma and hypothalamus [9]. Some cases of isolated histiocytosis X of the pituitary gland [14] or pituitary stalk [15,22] have also been reported. These cases showed no other symptoms or signs than central DI and hypopituitarism and it would not have been possible to diagnose correctly if a biopsy had not been performed. MRI findings of germinoma, chronic inflammation, and histiocytosis X are very similar: enlargement of part of the neurohypophyseal system, isointensity of the lesion on T1-weighted images, enhancement of the lesion with gadolinium- DTPA. Therefore, the differential diagnosis is very difficult by MRI only. The diagnosis in all three cases that underwent biopsy was nonspecific chronic inflammation. This is the first report of central DI resulting from localized chronic inflammation. We do not know what could have caused chronic inflammation localized in the neurohypophyseal tract, although it might be a case of autoimmune reaction [20]. The histological diagnoses for the other cases showing enlargement of the pituitary stalk (cases 2 and 4) may be chronic inflammation, in view of the good outcome even without treatment of the lesions and the spontaneous shrinkage we observed in case 2. From our results and those previously published in the literature, we can postulate that central DI frequently results from a nonneoplastic tiny mass lesion localized in the neurohypophyseal system.

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The authors have presented two cases that are unusual and well studied. They represent an entity that differs from the more typical lymphocytic hypophysitis, as pointed out by the authors. Is this a new entity, or is this perhaps responsible for some of the previously described "idiopathic diabetes insipidus"?

One must keep in mind that adenohypophyseal rests can occur along the infundibulum and basophil invasion may be seen in neurohypophysis. Therefore, it is possible that scant numbers of adenohypophyseal cells may be present in these locations, and the process depicted may represent true infundibulo-neurohypophysisitis.

This pathology affects a different age group and a different portion of the pituitary gland. Whether both represent an autoimmune phenomenon is yet to be determined. Both, however, can be treated medically with steroids and observation, unless there is acute neurologic dysfunction, such as visual loss requiring surgical decompression. If surgery is done, the authors point out that the anterior portion of the gland need not be excised and may recover some function. This is sound advice.

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THE TROUBLE WITH EICHMANN WAS PRECISELY THAT SO MANY WERE LIKE HIM, AND THAT THE MANY WERE NEITHER PERVERTED NOR SADISTIC, THAT THEY WERE, AND STILL ARE, TERRIBLY AND TERRIFYINGLY NORMAL. FROM THE VIEWPOINT OF OUR LEGAL INSTITUTIONS AND OF OUR MORAL STANDARDS OF JUDGMENT, THIS NORMALITY WAS MUCH MORE TERRIFYING THAN ALL THE ATROCITIES PUT TOGETHER.

HANNAH ARENDT (1906-75)
"EICHMANN IN JERUSALEM," EPILOGUE