Occult neurohypophyseal germinomas in patients presenting with central diabetes insipidus

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Although neurohypophyseal germinoma is known be a common initial symptom in cases of diabetes insipidus (DI), its radiological detection may take months or years even by a high-resolution magnetic resonance (MR) imaging. The term "occult neurohypophyseal germinoma" denotes such cases, but its clinical picture remains obscure.

Of seven patients with neurohypophyseal germinoma presenting with DI during the last 5 years, three patients showed no evidence of tumor at the onset of DI and were treated as "idiopathic" DI. Neurohypophyseal germinoma was eventually diagnosed in these three patients as the tumor became evident on sequential MR imaging studies and the patients were successfully treated with chemotherapy and radiation therapy. To delineate the clinical features of the occult neurohypophyseal germinoma, the authors analyzed endocrinological aspects and MR images in these patients and compared them with those in two patients with true idiopathic DI and four patients with overt neurohypophyseal germinoma and DI. Nine previously reported cases in the literature were reviewed. During the stage at which the germinoma gave no notable change on MR images, patients often displayed anterior pituitary dysfunction, particularly growth hormone (GH) deficiency, or an elevation of serum or cerebrospinal fluid human chorionic gonadotropin-beta. Preceding the appearance of an obvious tumor mass, a slight swelling of the pituitary stalk with loss of normal hyperintensity of the posterior pituitary lobe was a common finding on MR imaging.

Central DI associated either with an enlarged stalk, decreased GH secretion, or an elevated serum human chorionic gonadotropin-beta should prompt the diagnosis of an occult germinoma.

Key Words * diabetes insipidus * germinoma * hypothalamus * neurohypophysis * occult tumor

Central diabetes insipidus (DI) is the most common initial symptom of neurohypophyseal germ cell tumors, especially germinoma.[23,26,28,32] Occasionally DI precedes the emergence of radiological abnormalities that indicate a neurohypophyseal germinoma by several months or years.[2,4,5,20,22,26,28] Such germinoma causing DI has been termed "occult" germinoma. Although
rare, exclusion of this disease from the "idiopathic" central DI is necessary as well as the other treatable diseases.[6,12,37] To our knowledge, nine children with the occult germinoma have been reported in the literature, of which four were evaluated using computerized tomography (CT) scanning and the other five by using magnetic resonance (MR) imaging.[2,4,5,20,22,26,28] This report adds three cases of children with occult neurohypophyseal germinoma and central DI, and we review the literature to discuss the diagnostic difficulties in the early detection of an evolving germinoma to improve patient outcome.

CLINICAL MATERIAL AND METHODS

Between 1993 and 1998, 24 patients with histologically verified germinoma were treated in the Hokkaido University Hospital. Among them, seven children and adolescents (six boys and one girl, aged 8-18 years) had a solitary neurohypophyseal germinoma, and all presented with central DI as an initial manifestation. Because these patients presented with polyuria and polydipsia, their central DI was evaluated by either a water-deprivation test or measurement of simultaneous urinary and serum osmolality.

In three of the seven patients, MR or CT images, obtained at disease presentation, were originally interpreted as normal, except for the absence of high signal intensity in the posterior pituitary lobe. Idiopathic central DI was the initial diagnosis. The ages at onset of DI in the three children were 14, 9, and 10 years, and the intervals between presentation and radiological evidence of mass lesions were 50, 19, and 8 months, respectively (Table 1). During the same period, idiopathic DI was diagnosed in five children at the Hokkaido University Hospital, thus the three children comprised 60% of the five cases of idiopathic DI. The remaining two patients with true idiopathic DI did not show anterior pituitary dysfunction, stalk hypertrophy, or elevated serum human chorionic gonadotropin-beta (HCG-beta) or alpha-fetoprotein. The diagnosis of idiopathic central DI was based on endocrinological examinations and neuroradiological images that were interpreted as normal.

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<td>GH</td>
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* FSH = follicle-stimulating hormone; LH = luteinizing hormone; ND = not described; TSH = thyroid-stimulating hormone.
† Interval in months between onset of DI and detection of the tumor.
‡ Interval in months between onset of DI and detection of the anterior pituitary dysfunction.
RESULTS

Twelve and 6 months prior to the diagnosis of tumors in two patients, respectively, a low-intensity signal lesion was observed on MR imaging of the posterior pituitary lobe; one patient later showed an enlarged pituitary stalk. At the time of surgery and histological examination of the tumor, two patients had solitary disease with or without elevated levels of serum HCG-beta, and one had multifocal disease with a normal level of HCG-beta. Transsphenoidally obtained biopsy samples in two patients and a CT-guided stereotactic biopsy sample in one patient were revealed to be pure germinomas. The three patients showed anterior pituitary hormone deficiencies; two of them (Cases 1 and 3) showed a decreased secretion of growth hormone (GH) 28 and 8 months prior to the histological diagnosis, respectively.

The three patients were treated with four cycles of chemotherapy prior to receiving localized radiation therapy according to our treatment protocol, as described elsewhere.[31] At the final follow-up observation, the tumors of all three children were progression free. During the entire follow-up period, no neurological or endocrinological deterioration related to the therapy was observed.

CASE PRESENTATION

Case 1

This 18-year-old man was hospitalized for treatment of a neurohypophyseal lesion. Idiopathic DI had been diagnosed in this patient when he was 14 years of age, in April 1991. Evaluation by CT scanning in September 1991 revealed normal configuration of the hypothalamic-pituitary axis including the pituitary stalk (Fig. 1 upper). No other physical, neurological, or endocrinological abnormalities were demonstrated at that time. In August 1993, 28 months after onset of DI, endocrinological examination demonstrated decreased levels of GH, somatomedin C, luteinizing hormone, and follicle-stimulating hormone. His anterior pituitary dysfunction worsened in December 1993. In June 1995, 50 months after onset of DI, MR imaging revealed a mass lesion in the sella turcica extending to the third ventricle (Fig. 1 lower left). The level of HCG-beta was normal in both serum and cerebrospinal fluid (CSF). A biopsy sample was obtained via the transsphenoidal route. On histological examination, the sample was identified as pure germinoma. The patient received four cycles of etoposide and cisplatin chemotherapy, followed by a 24-Gy dose of localized radiation. The patient has been tumor free with persistent panhypopituitarism and DI for 27 months after the treatment. A follow-up MR image showed an atrophic hypophysis (Fig. 1 lower right).
Fig. 1. Case 1. Upper: Contrast-enhanced axial CT scan obtained at onset of central DI, showing the normal size of pituitary stalk (arrow). Lower Left: An MR image obtained 50 months later depicting an abnormal enhanced mass in the pituitary fossa extending along the pituitary stalk and to the hypothalamus. The anterior pituitary lobe is compressed by the mass toward the anterior wall of the sella turcica. Lower Right: A follow-up MR image obtained 27 months after chemotherapy and radiation therapy showing atrophy of the hypophysis; the patient was tumor free.

Case 2

This girl first presented with polyuria and polydipsia at the age of 9 years. The first MR image obtained just after onset of DI was evaluated as normal. Endocrinological examinations indicated central DI with anterior pituitary dysfunction. Follow-up MR imaging 7 months after onset of DI (October 1993) demonstrated low signal mass lesion involving the stalk and the posterior lobe of the pituitary gland. On MR imaging performed 12 months later, (October 1994), an abnormal enhanced mass was observed spreading from the neurohypophyseal region to the anterior half of the third and bilateral ventricle walls. Levels of HCG-beta in the serum and CSF were not elevated. A CT-guided stereotactic biopsy specimen obtained from a mass in the lateral ventricle wall was revealed on histological examination to be pure
germinoma. The patient was treated with four cycles of ifosphamide, cisplatin, and etoposide chemotherapy, followed by a 24-Gy dose of localized radiation. A complete response was achieved after the first chemotherapy cycle. The patient has been free of tumor for 37 months, but DI and anterior pituitary dysfunction have remained.

**Case 3**

This 10-year-old boy with a 2-month history of polyuria and polydipsia was referred to our hospital. Initial MR imaging showed the normal anatomy of the hypothalamic-hypophyseal axis, except for a loss of the normal hyperintensity of the posterior pituitary lobe (Fig. 2 left and center). The level of HCG-beta was under the detection limit (0.5 mIU/ml). Four months later, follow-up MR imaging revealed a slight thickening of the pituitary stalk and an abnormal enhancement of the tuber cinereum (Fig. 2 right).

![Fig. 2. Case 3. Left and Center: Two T1-weighted MR images obtained at onset of central DI, showing the absence of the high signal intensity in the posterior pituitary lobe (left; no contrast medium) and no abnormal enhancement of the pituitary stalk (center; with gadolinium). Right: A follow-up contrast-enhanced MR image obtained 4 months later showing the stalk to be slightly thickened and shifted anteriorly due to compression by a mass lesion in the pituitary fossa.](image)

Endocrinological reexaminations in February 1997 demonstrated a decreased level of GH secretion in response to an arginine loading test, and the patient required increased doses of desmopressin (5 mg/day) to control DI. At this time, we considered that obtaining a biopsy sample of the slightly swollen stalk would be harmful to the remaining hypophyseal functions. Two months later, the third MR imaging study showed the pituitary stalk had thickened, with an enhanced mass occupying the posterior part of the pituitary fossa (Fig. 3 left). Moreover, HCG-beta in serum and CSF turned positive. Examination of a transsphenoidally obtained biopsy sample (March 1997) verified the diagnosis of pure germinoma (Fig. 3 right).
The boy received four cycles of ifosfamide, cisplatin, and etoposide chemotherapy, followed by a 24-Gy dose of local radiation. A complete response with normalization of the HCG-beta level was achieved by the first chemotherapy treatment (Fig. 4). The DI improved with a decreased dose of desmopressin (0.5 mg/day). He has remained tumor free for 10 months and grew normally in height from 140.7 to 143.6 cm without GH replacement for the 6 months after the therapy.

**DISCUSSION**

The absence of abnormality on radiological studies in cases of central DI caused by an occult tumor may result in a critical delay in the accurate diagnosis and therefore in the appropriate treatment of diseases. The radiologically "occult" hypothalamoneurohypophyseal tumors that have been described in the literature include germinomas,[2,4,5,20,22,26,28] immature teratomas,[17] metastatic carcinomas,[24]
Germinomas have an almost exclusive predominance as the "occult" cause of DI in teenagers.[9,15,23] In their course, occult neurohypophyseal germinomas may display subtle radiological changes before forming an obvious mass tumor. As seen in our Cases 2 and 3, those changes are thickening of the pituitary stalk and lack of normal hyperintensity of the pituitary posterior lobe. The normal hyperintensity of the posterior lobe uniformly seen in healthy children on T1-weighted MR images is thought to reflect protein-rich neurosecretory granules.[8,10,13,21] Any organic lesions that can cause central DI, (that is, the interruption of the synthesis and/or axonal transport of posterior pituitary hormones along the hypothalamo-infundibulo-neurohypophyseal pathway) may nonspecifically cause the lack of the hyperintensity.[2,7,8,13,18,21,30,35,36] In the absence of an apparent hypothalamic lesion, however, the emergence of this sign in young patients with central DI most probably indicates an occult hypophyseal germinoma.[9,23,25,34,35]

A thickened pituitary stalk in patients with central DI necessitates differential diagnosis that includes Langerhans' cell histiocytosis,[36] lymphocytic hypophysitis involving the infundibulum, neurosarcoidosis, tuberculosis, adenoneurohypophysitis of another category,[14,16,19] infiltration from adjacent neoplasms, and metastasis. Neoplastic infiltration and metastasis are radiographically distinguishable from regional or systemic findings. For neurosarcoidosis and tuberculosis, chest x-ray studies and immunological and serological examinations will provide diagnostic information.

Infundibulohypophysitis can be distinguished from occult germinoma by the presence of an enhanced pituitary lesion and its frequent association with pregnancy in female patients.[16] However, the Langerhans' cell histiocytosis may take a course quite similar to an occult germinoma.[3,29] Findings on MR imaging of the hypophyseal histiocytosis also demonstrate a homogenously enhanced, thickened stalk and absent posterior pituitary hyperintensity.[11,36] Systemic bone lesions should be searched, but in cases of solitary hypophyseal lesion, obtaining a biopsy sample is mandatory.[11,36]

Another important feature of occult neurohypophyseal germinoma is dysfunction in secretion of the anterior pituitary hormones, particularly GH, as seen in our three cases and many of the previously reported cases. Review of the literature disclosed nine reported cases of occult neurohypophyseal germinoma. Among them, six showed anterior pituitary dysfunction, particularly of GH secretion before or at diagnosis. Elevated levels of HCG-beta were described in two cases (Table 1). Notably, the deficiency of GH secretion on stimulation often preceded the obvious tumor mass formation. This is in contrast with anterior hypophyseal deficiency caused by tumor infiltration that occurs rather in the late stage of usual suprasellar (hypothalamic) germinomas.[1,17,23,33] The association of central DI with evolving anterior pituitary endocrinopathy thus points to the presence of an occult neurohypophyseal germinoma.[32] Elevated levels of HCG-beta and/or human placental alkaline phosphatase should greatly enhance suspicion of the disease. Because the tumor marker is often more sensitive than detectable changes in images,[4] if present, it is an important clue for the diagnosis of an occult germinoma.

It was previously considered that endocrinological dysfunctions manifested in germinoma cases could not be ameliorated even after patients undergo successful radiotherapy with a dose exceeding 40 Gy delivered to the tumor.[1,17,33] Several authors suggested that the radiation-induced damage to the hypothalamic-pituitary unit might be avoided by proper use of chemotherapy.[1,17,33] It has been recently demonstrated that intracranial germinomas can be cured efficiently by chemotherapy in combination with radiation therapy with a localized dose of 24 Gy.[31] Kumanogoh, et al.,[17] have
indicated that anterior pituitary dysfunction by germinomas was reversible after successful chemotherapy, whereas they failed to improve DI.[17] In our Case 3, however, DI as well as anterior pituitary dysfunction were improved after chemotherapy-based treatment with a limited dose of radiation. Analysis of these results suggests that the endocrinological symptoms, and even DI itself, are not irreversible when an appropriate treatment is provided within several months after onset of disease. Early diagnosis of the disease and early chemotherapy-based treatment thus may favor endocrinological outcomes for patients with germinoma in the neurohypophyseal region. We therefore propose that an early biopsy sample obtained for histological verification should be considered in cases of children or adolescents who present with DI and the previously mentioned hallmark characteristics of the occult hypophyseal germinomas, avoiding a delay by close follow-up endocrinological and MR studies.

References


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