Hypothalamic hamartoma

Report of two cases

SHUNJI NISHIO, M.D., SHIGERU FUJIWARA, M.D., YASUTAKA AIKO, M.D., IWAO TAKESHITA, M.D., AND MASASHI FUKUI, M.D.

Department of Neurosurgery, Neurological Institute, Faculty of Medicine, Kyushu University, Fukuoka, Japan

Two cases of hypothalamic hamartoma are presented. The first patient was a 4-year-old boy with precocious puberty, and the second was a 6-year-old boy with epileptic seizures. In both patients, clinical symptoms and signs appeared at the age of 2 years and progressed thereafter. Computerized tomography and magnetic resonance imaging in both cases disclosed a suprasellar mass lesion in continuity with the hypothalamus. Removal of the lesions affected the endocrinological status and/or seizure control. Pathological examination revealed the lesions to be composed of well-differentiated neuronal and glial cells. Immunohistochemical study demonstrated the presence of beta-endorphin, corticotropin-releasing factor, oxytocin, and neurofilament protein (210 kD) in the neuronal cells of the first patient, but no neuropeptides were detected in the second. Electron microscopic examination on the second patient disclosed the presence of many nonmyelinated and some myelinated neuronal processes containing dense-core and clear vesicles. The morphological characteristics and the role of surgery for this lesion are discussed.

KEY WORDS • hypothalamic hamartoma • precocious puberty • cerebral seizure • magnetic resonance imaging • neuropeptide

HAMARTOMA has been defined as a benign nodular or tumor-like mass composed of a mixture of differentiated tissues normally present in the organ in which it occurs, but in an abnormal location. In the central nervous system (CNS), this lesion is a relatively rare occurrence and is usually encountered in proximity to the hypothalamus. Clinically, most of the published cases of hypothalamic hamartoma were associated with precocious puberty and/or epilepsy. Although surgical treatment for these conditions has been considered to be of little benefit, a good response to surgery has been reported recently.

We report our surgical experience with two cases of hypothalamic hamartoma. These two cases also offer support for considering surgical treatment.

Case Reports

Case 1

This 4-year-old boy had been well until the age of 2 years 5 months, when his parents noticed the presence of pubic hair and excessive growth of external genitalia. His height had also rapidly increased. At the age of 3 years, he was initially seen at our municipal Children’s Hospital. Endocrinological studies revealed him to have precocious puberty of central origin. There was an increase in basal serum levels of testosterone (6.8 ng/ml; normal 0.03 to 0.11 ng/ml), follicle-stimulating hormone (FSH, 6.1 mIU/ml; normal 4.4 to 4.8 mIU/ml), and luteinizing hormone (LH, 11.0 mIU/ml; normal 2.1 to 2.7 mIU/ml). The response of LH to intravenous injections of LH-releasing hormone (LH-RH) showed a pathological response, which was pubertal in pattern and magnitude (Fig. 1A). The serum level of prolactin was 7.4 ng/ml. The thyroid-stimulating hormone and growth hormone secretions were normal. The patient was placed on a course of cyproterone acetate.

Admission. Seven months later, the patient developed gynecomastia, and the serum prolactin level increased to 32.5 ng/ml (normal 3 to 15 ng/ml). Computerized tomography (CT) demonstrated a round isodense mass attached to the hypothalamus and occupying the suprasellar cistern. He was admitted for surgery. He was large for his chronological age of 4
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FIG. 1. Results of preoperative (solid lines) and postoperative (dotted lines) endocrinological testing for luteinizing hormone (LH) after LH-releasing hormone stimulation in Case 1 (A) and Case 2 (B).

years 4 months. He had prominent pubic hair, a large penis and testes, and gynecomastia. Neither axillary hair nor other signs of secondary sexual characters were observed. Neurological examination was normal. He did not have seizures. Magnetic resonance (MR) imaging of the brain demonstrated a round, mostly iso-intense mass with some high intensity attached to the hypothalamus on both the T1- and T2-weighted images (Fig. 2).

Operation. At surgery, a round mass was found filling the suprasellar region and attached to the hypothalamus behind the pituitary stalk. Most of the mass, which was grayish-white and looked like normal brain, was removed, but a small amount was left behind on the side of the hypothalamus (Fig. 2).

Postoperative Course. The patient’s course was uneventful, and his gynecomastia disappeared within 1 week after surgery. At 1 month after surgery the serum levels of testosterone and prolactin decreased to 0.5 ng/ml and 13.0 ng/ml, respectively. No apparent clinical change of sexual precocity was noted, however, and 3 months later studies showed a rise in serum levels of testosterone, FSH, and LH. Since then he has been treated with cyproterone acetate again, which has improved his endocrinological status.

Case 2

This 6-year-old boy had shown normal physical and mental development until the age of 2 years 6 months, when he developed episodic unconsciousness and laughing attacks, which were diagnosed as psychomotor seizures. Endocrinological examinations at 3 years 9 months revealed no abnormal findings. He gradually developed disturbances of memory, behaved abnormally, and became indifferent to his surroundings. Seizures occurred more than 10 times a day and their control was difficult. When he was 6½ years old, he was admitted to our service.

Admission. Neurologically, mental retardation and behavioral disturbances were noted. The patient could not play with other children or communicate well even with his mother. The character of the seizures varied among grand mal, petit mal, akinetic, Jacksonian, partial complex, or infantile spasm. There were no signs of precocious puberty. On CT and MR imaging a mass was revealed originating from the undersurface of the

FIG. 2. Magnetic resonance images (spin echo: TR 2000 msec, TE 50 msec) in Case 1. Left: Preoperative study showing a mixed-intensity mass connecting with the hypothalamus (arrows). Right: Postoperative study showing a small amount of the hamartoma remaining (arrows).
hypothalamus and extending into the suprasellar and interpeduncular cisterns on the left. On CT, no contrast enhancement of the isodense mass was demonstrated. On MR imaging, the mass was isointense with some high intensity on T1-weighted images (Fig. 3). On T2-weighted images, the lesion was of high intensity. Pentobarbital-induced sleep electroencephalography (EEG) showed multifocal paroxysmal sharp wave bursts. The endocrinological examinations demonstrated increased serum levels of LH (5.7 mIU/ml; normal 2.1 to 2.7 mIU/ml) and testosterone (89.0 ng/ml; normal 4.3 to 11.5 ng/ml). The response of LH to LH-RH test was pubertal in pattern and magnitude (Fig. 1B).

Operation. The operative approach was through frontotemporal craniotomy and the mass was totally removed (Fig. 3). Macroscopic appearance was consistent with that of a hypothalamic hamartoma.

Postoperative Course. The postoperative course was uneventful, and the epileptic seizures subsided except for several episodes of generalized seizures, which occurred within 3 weeks after surgery. Postoperative EEG showed marked improvement. Endocrinological improvement was also marked, and the serum levels of LH and testosterone decreased to 3.2 mIU/ml and below 0.3 ng/ml, respectively. The LH-RH test also improved (Fig. 1). Mental and verbal functions have improved; he has become able to communicate, although with impediment, and play with other children at kindergarten. The total doses of anticonvulsant drugs required also have decreased. At the time of writing the boy is 7\(\frac{1}{2}\) years old and is seizure-free.

Anatomic Pathological Features

The general histological features of the excised tissue were similar in both cases and resembled those of normal gray matter. The masses were composed of aggregates of well-differentiated neurons, which varied in shape and were irregularly distributed (Fig. 4). Neuronal cell processes ran irregularly, except for some areas, where they formed a bundle. Astrocytes and oligodendrocytes were loosely scattered in a fibrillary matrix. Neither mitotic figures nor binucleated forms of neurons were found. The fibrous connective tissue and vascular stroma were not prominent within the masses. Immunohistochemical study using antisera against beta-endorphin, dynorphin, neurophysin, oxytocin, vasopressin, and corticotropin-releasing factor (CRF) in both cases and neurofilament proteins (68 kD, 160 kD, and 210 kD) in Case 1, were performed using the method described elsewhere. Beta-endorphin, CRF, oxytocin, and neurofilament protein (210 kD) were identified in some neurons and neuronal processes in Case 1 (Fig. 4), but none of the neuropeptides was positive in Case 2.

Electron microscopic examination on Case 2 disclosed the presence of neurons and glial cells in the lesion (Fig. 5). In the perikaryon of the neurons, many round membrane-bound lysosomes varying in size were present. Many nonmyelinated and occasional myelinated neuronal processes containing numerous clear vesicles, some dense-core vesicles, and microtubules were found. Synaptic formation was noted, but the collagen fibers were not present. Capillary blood vessels did not show fenestration or gap junction.

Discussion

Although hamartomas of the CNS are considered to result from faulty embryonal development of cells and tissues, the confines of the term “hypothalamic hamartoma” have been confusing. In addition,
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Hamartomas may undergo neoplastic transformation, and transitional forms between nonneoplastic hamartomatous lesions and gangliogliomas have been described. The midline spherical bodies arising from the floor of the third ventricle and the recapitulation of disorderly, but mature and differentiated neuronal elements native to the region exclude a neoplastic process in the strict sense, and allow designation of these lesions as the classical type of hypothalamic hamartoma. The current report presents data with immunohistochemical and ultrastructural findings.

In most cases, hamartomas have an anatomical connection with the tuber cinereum or mamillary body, usually by way of a distinct stalk, although they can be unattached or have more than one attachment to the hypothalamus. Although some authors have claimed no similarity between neurons of hypothalamic hamartoma and those of the hypothalamus, the resemblance of these lesions to the adjacent hypothalamus on morphological and hormonal bases has been repeatedly stressed. In Case 1, neurons exhibited beta-endorphin, CRF, and oxytocin, which are contained in high concentration in the hypothalamus. The demonstration of multiple neuronal populations based on neuropeptide patterns suggests that some neurons in our cases have functional similarities to the hypothalamic neurons, and may also indicate the hamartomatous nature of our lesion. Some neuronal neoplasms, including ganglioglioma, have also been shown to have neuropeptides, which are characteristic of the hypothalamus. In addition, some neuronal elements in our hamartoma showed positive immunohistochemical reaction for a 210-kD neurofilament protein, a positivity found only in some processes of Purkinje cells in the normal cerebellum and in some neoplastic cells of a ganglioglioma, pineocytoma, and subependymal giant cell astrocytoma (unpublished data). Hypothalamic hamartomas may be linked with the gangliogliomas, some of which may be organized in a very similar manner despite their very different growing potential.

One of our patients had manifestations of precocious puberty, and the other showed endocrinological abnormalities consistent with this condition without the clinical manifestations. The percentage of hamartomas presenting with precocious puberty is not known, and the relationship between hamartomas and clinical symptoms remains uncertain. However, several theories...
have been proposed to explain the development of precocious puberty in this disease. Recently, the presence of LH-RH in the neurons of a hamartoma has been demonstrated in some cases. In other cases, the hypothalamic gonadotropin-releasing hormone secreting center may be stimulated via myelinated fibers connecting the hamartoma and the hypothalamus. The control mechanism of the hypothalamus may also be disrupted through compression of the tuber cinereum by the hamartoma. Some neurons in the hamartoma presented here bear a resemblance to those of the hypothalamus, as indicated above. Ultrastructurally, we confirmed the rare presence of myelinated fibers in the hamartoma. Gynecomastia and elevated serum prolactin levels, which were improved or normalized after removal of the lesion in Case 1, may be the result of mechanical compression of the pituitary stalk or hypothalamus by the hamartoma. Hamartomas may influence hypothalamic and/or pituitary function by one or more of these mechanisms.

Computerized tomography has been a useful diagnostic method for localizing and defining masses in the area of the hypothalamus. Hypothalamic hamartomas are usually detected as an abnormal fullness of the interpeduncular, preopticine, and posterior suprasellar cisterns, with distortion of the anterior third ventricle in some cases. There is usually no enhancement of the lesion following contrast administration. Magnetic resonance imaging also enables good coronal and sagittal imaging, which delineates the lesion and its anatomic relationship to the hypothalamus. At this early stage of MR imaging experience, it is not certain whether all hypothalamic hamartomas show the same signal pattern. Peterman, et al. reported that these lesions had a T1 similar to that of the gray matter and a slightly increased T2. The MR images of our two cases showed almost the same signal behavior with mixed echo intensity on both T1- and T2-weighted images. Magnetic resonance imaging will become the most useful neuroradiological study for this lesion.

The efficacy of surgical treatment for the endocrinological syndrome or cerebral seizures has been controversial. With recent advances in microsurgical technique, however, patients with endocrinological improvement after surgery have been reported. Amelioration of cerebral seizures has also been noted. Separation of a possible neuronal connection between the neurons of the lesion with those of the limbic system may explain the improvement in seizures after surgery. Complete removal of temporal gangliogliomas has also been reported to have produced a dramatic improvement in seizure control. In our Case 1, partial removal of the lesion was followed only by a temporary endocrinological improvement. In Case 2, both cerebral

![Image](image_url)

FIG. 5. Electron microscopic features of the hamartoma in Case 2. Left: Irregularly-shaped lysosomes, microtubules (closed arrows), and dense-core vesicles (open arrows) are seen in the cytoplasm, x 22,000. Upper Right: View of a synapse. Numerous clear vesicles and dense-core vesicles are seen. x 28,000. Lower Right: View of a myelinated and an unmyelinated (arrow) neuronal processes. The latter contains parallel bundles of microtubules and dense-core vesicles, x 11,000.

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seizures and endocrinological abnormalities markedly improved after total removal of the lesion. The difference in surgical effects may be due to the amount of the lesion removed.

Although the effect of surgery is not certain and cannot be predicted preoperatively, these observations must be weighed in the consideration of surgical management when a patient has uncontrollable endocrinological and/or seizure disorders causing psychiatric or social problems.\(^2,5,6\) Currently available medical therapy, including medroxyprogesterone acetate and cyproterone acetate, is not entirely satisfactory in controlling precocious puberty,\(^6\) and long-term experience with these drugs is not yet available.

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References