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Case Report

Two Cases of Precocious Puberty Associated with Hypothalamic Hamartoma

Shigeru Nagaki[1], Eiko Otsuka[1], Kumiko Miwa[1], Makoto Funatsuka[1], Osami Kubo[2], Tomokatsu Hori[2], Noriyuki Shibata[3], Tatsuo Sawada[3], and Makiko Osawa[1]

[1]*Department of Pediatrics, Tokyo Women's Medical University, Tokyo, Japan*

[2]*Department of Neurosurgery, Tokyo Women's Medical University, Tokyo, Japan*

[3]*Department of Pathology, Tokyo Women's Medical University, Tokyo, Japan*

Abstract. Hypothalamic hamartoma (HH) is a congenital malformation diagnosed based on magnetic resonance imaging (MRI) and histological findings; it is often associated with central precocious puberty (CPP), gelastic seizures, abnormal behavior and mental retardation. In the present paper, we report our retrospective hypothesis that there is a relationship between symptoms and therapy, as well as the treatment for HH, and describe two cases of HH associated with CPP. Both cases had sessile masses located in the interpeduncular cistern, with extension to the hypothalamus on MRI (1.2 × 1.5 cm and 2.0 × 2.5 cm, respectively). The first case had intractable seizures, while the second had no seizures with paroxysmal discharge. In both patients, the hamartomas were partially removed, by γ-knife and surgical operation in the first case and surgically in the second, and a gonadotropin releasing hormone (GnRH) analogue was prescribed. One case showed improvement of both intelligence quotient (IQ) score and seizures, and the other showed improvements in IQ and abnormal behavior. It was difficult to determine any topology/symptom relationships. Surgery and GnRH analogue treatment can alleviate seizures, abnormal behavior and mental retardation associated with HH.

Key words: hypothalamic hamartoma, precocious puberty, gonadotropin releasing hormone analogue, magnetic resonance imaging, mental retardation

Introduction

Hypothalamic hamartoma (HH) is a congenital malformation that usually originates close to the tuber cinereum and mamillary bodies; it has a sessile or pedunculated attachment, extends into the interpeduncular cistern and sometimes bulges into the floor of the third ventricle (1, 2). HH is diagnosed based on magnetic resonance imaging (MRI) and histological findings; it is often associated with central precocious puberty (CPP), gelastic seizures, abnormal behavior and mental retardation (2, 3).

CPP in HH patients may start at a very young age, in some cases even at birth (3, 4). Treatment with a gonadotropin-releasing hormone (GnRH) analogue is reportedly effective in patients with gonadotropin-dependent precocious puberty and HH (5, 6).

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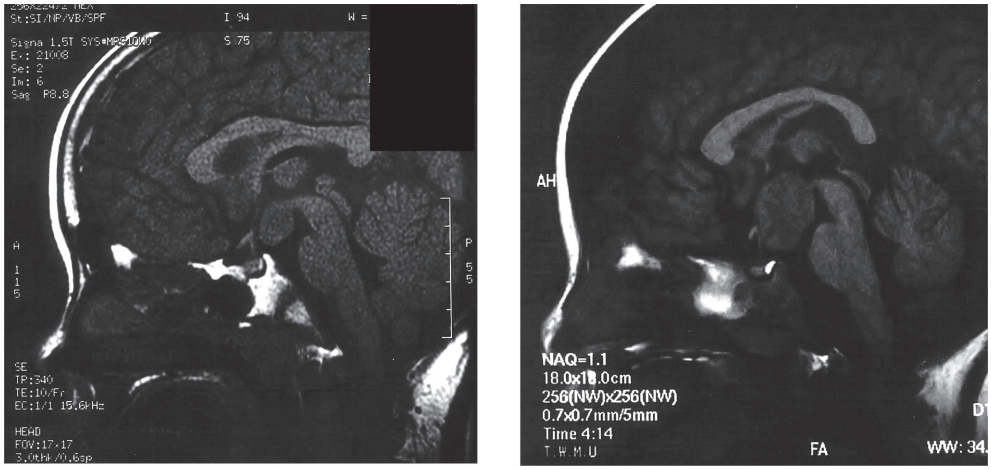
Correspondence: Dr. Shigeru Nagaki, Department of Pediatrics, Tokyo Women's Medical University, 8-1 Kawadacho, Shinjuku-ku, Tokyo 162-8666, Japan
E-mail: snagaki@ped.twmu.ac.jp



(a) (b)

Fig. 1 MRI findings (T1-weighted sagittal images) from cases 1 (a) and 2 (b). The lesions (1.2 × 1.5 cm in Case 1; 2.0 × 2.5 cm in case 2), which are protruding into the interpeduncular cistern, are isointense to gray matter and distort the third ventricle.

Case Report

Case 1

This patient was a boy at 7 yr and 11 mo of age. He was born at a gestational age of 40 wk to nonconsanguineous parents. Pregnancy and delivery were uneventful. At birth, his length was 51 cm and his weight was 3,500 g. He had gelastic seizures starting in the neonatal period, but his parents did not recognize them. At the age of 3 yr and 8 mo, he underwent an EEG examination, and epilepsy was diagnosed. On admission to our hospital, his height was 102.4 cm (+0.71 SD)and his weight was 14.8 kg (–0.35 SD). His brain MRI demonstrated an isointense hypothalamic mass of the tuber cinereum. The tumor mass was sessile and 1.2 × 1.5 cm in diameter,and it involved the hypothalamus and distorted the third ventricle (Fig. 1 (a)). The patient was treated with antiepileptic drugs (valproic acid and clonazepam), but his epileptic attacks remained intractable. At the age of 4 yr and 11 mo, he was treated with a γ-knife, and his drop attacks disappeared, but his gelastic seizures did not change. Later, a hormonal examination showed a high serum testosterone level (149.0 ng/dl). On a subsequent LH-RH loading test, his LH and FSH responses showed a pubertal pattern (Table 1). At the age of 6 yr, enlargement of the testes and penis was observed; his testicular volume was 5 ml, penis Tanner stage II and bone age (BA) was 8 yr at a chronological age (CA) of 6 yr and 3 mo. He was treated with a GnRH analogue (40 μg/kg) every 4 wk for 7 mo, starting at 6 yr and 4 mo of age. After 3 mo of GnRH analogue treatment, the LH, FSH and testosterone levels were suppressed. At the age of 7 yr, he was treated with partial surgical removal of the HH because of intractable seizures. Histopathological examination showed that the resected tumor tissue was composed of numerous small neurons, as well as mature ganglion cells and glial cells. The small neurons had scanty cytoplasm and the other cells were immature with a partially atrophic pattern. Some astrocytes showed reactive changes with scattered calcifications. These neurons had neither a heteromorphic nor dysplastic pattern. Immunohistochemical staining with LH-RH antibody was positive in neurons and endothelial

Table 1 Laboratory findings of Cases 1 and 2

Case 1

(At the age of 5 yr and 10 mo)		(normal range)
ACTH	41.1 pg/ml	(10–60)
Cortisol	8.6 μg/dl	(4.5–24)
TSH	3.78 μIU/ml	(0.53–4.43)
fT3	3.98 pg/ml	(2.28–4.11)
fT4	1.06 ng/dl	(0.94–2.00)
Testosterone	149.0 ng/dl	(<5.0)
IGF-1	225 ng/ml	(50–290)

LH-RH loading test (At the age of 6 yr and 3 mo)		(normal range)
	LH (mIU/ml)	FSH (mIU/ml)
Before	3.7 (0.02–0.44)	5.6 (0.18–2.58)
After 30 min	24.5	7.9
After 60 min	25.0	9.7
After 90 min	20.9	8.9
After 120 min	17.0	8.8

(At the age of 6 yr and 10 mo)	
LH	0.4 mIU/ml
FSH	<0.4 mIU/ml
Testosterone	<5.0 ng/dl

Case 2

(At the age of 1 yr and 6 mo)		(normal range)
ACTH	42.0 pg/ml	(10–60)
Cortisol	14.4 μg/dl	(4.5–24)
TSH	2.42 μIU/ml	(0.53–4.43)
fT3	2.41 pg/ml	(2.28–4.11)
fT4	1.17 ng/dl	(0.94–2.00)
Testosterone	459.3 ng/dl	(<5.0)
IGF-1	253 ng/ml	(22–160)

LH-RH loading test (At the age of 1 yr and 7 mo)		(normal range)
	LH (mIU/ml)	FSH (mIU/ml)
Before	1.9 (0.02–0.44)	4.4 (0.18–2.58)
After 30 min	24.6	7.7
After 60 min	20.8	8.4
After 90 min	17.1	8.6
After 120 min	13.9	8.5

(At the age of 3 yr and 10 mo)	
LH	0.3 mIU/ml
FSH	<0.5 mIU/ml
Testosterone	<5.0 ng/dl

cells of capillary walls (Fig. 2 (a)). After the operation, the epileptic attacks disappeared, and GnRH analogue treatment was restarted at a CA of 7 yr and 7 mo because his pubertal symptoms reappeared. His growth chart is shown in Fig. 3 (a). His intelligence quotient (IQ) score on the Wechsler Intelligence Scale for Children (WISC) improved from 66 (verbal IQ (VIQ), 68; performance IQ (PIQ),71) to 86 (VIQ 82, PIQ 93) after the operation and GnRH analogue treatment.

Case 2

This patient was a boy at 4 yr and 10 mo of age. At the age of 7 mo, his height and weight growth accelerated and pubic hair appeared. MRI showed an isointense hypothalamic mass of the tuber cinereum, and HH was diagnosed. The mass was sessile and 2.0 × 2.5 cm in diameter, and it involved the hypothalamus and distorted the third ventricle (Fig. 1 (b)). The patient did not show overt epileptic attacks, but a spike in the right central region was detected on EEG. Antiepileptic drugs were not prescribed. At a CA of 1 yr and 6 mo, he showed behavioral abnormalities, including hyperactivity and aggression, and his height and weight were 91.8 cm (+3.32 SD) and 17.2 kg (+5.82 SD), respectively. His testes were enlarged (5–6 ml), pubic hair Tanner stage was II, serum testosterone levels were elevated (459.3 ng/ml) and BA was 7 yr. His serum LH and FSH levels were in the pubertal range both before and after the LH-RH loading test (Table 1). CPP was diagnosed, and he was started on treatment with a GnRH analogue (50 μg/kg) every 4 wk. Three months after GnRH analogue treatment, his gonadotropin and testosterone levels were suppressed. The patien's physical pubertal signs also showed gradual suppression. At the age of 1 yr and 11 mo, surgery to partially remove the HH was performed. Histopathology showed atrophic and irregular round neurons, with some parts consisting of mature ganglion cells. GFAP(glial fibrillary acidic protein) positive astrocytes

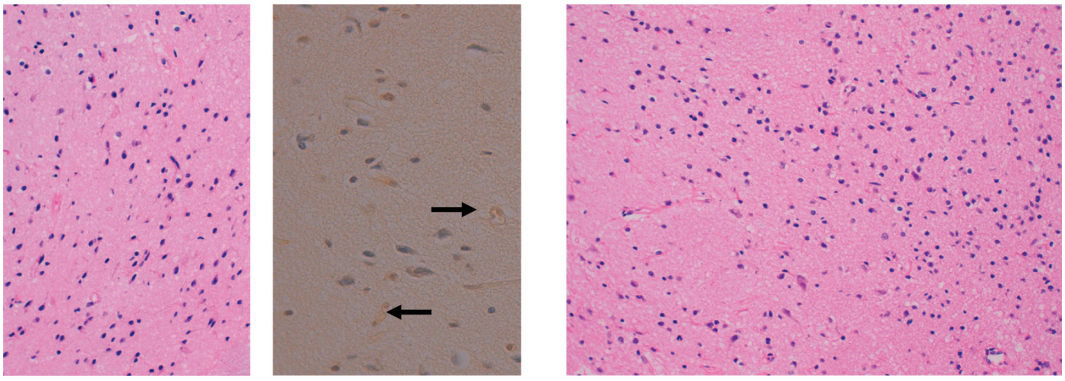


Fig. 2 Histopathology of cases 1 (a) and 2 (b). Left (a) H.E. (× 200). Right (a) LH-RH stain (arrow shows LH-RH positive area). (b) H.E. (× 200).

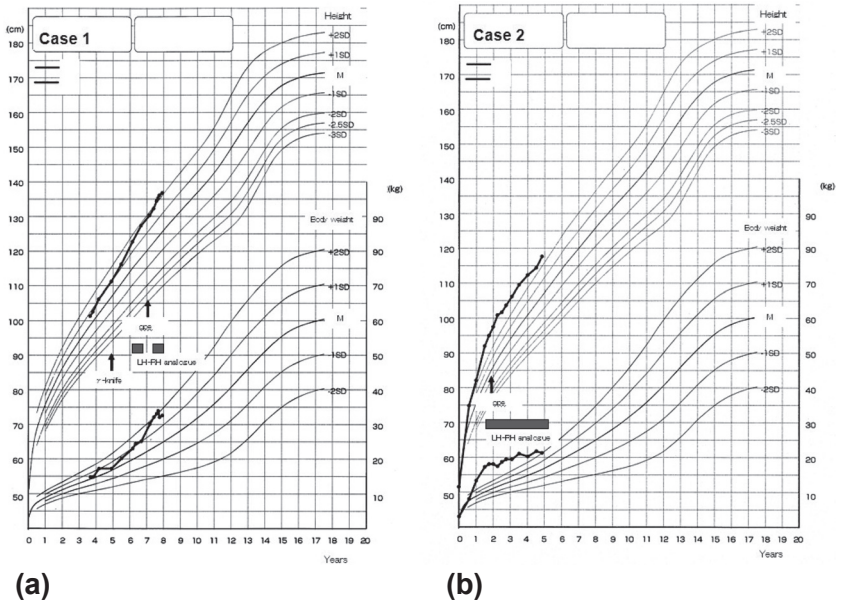


Fig. 3 Growth charts for cases 1 (a) and 2 (b).

showed no significant proliferative or heteromorphic characteristics. His MIB-1 score was thus 0.7 percent. Immunohistochemical staining with LH-RH antibody was not performed (Fig. 2 (b)). His growth chart is shown in Fig. 3 (b). After surgical removal of the HH and GnRH analogue treatment, his abnormal behavior and DQ (developmental quotient)/IQ scores were improved, from a DQ of 86 by the Tsumori Inage test before the operation to an IQ of 116 by the TK Binet intelligence test after the operation and GnRH analog treatment.

Discussion

Two cases of CPP associated with HH diagnosed by MRI and histological findings are described in this report. Berkovic *et al.* first described the syndrome of gelastic seizures, HH and mental retardation and estimated its

prevalence to be 1 in 50,000 to 100,000 (7). The most probable signs indicating a diagnosis of HH include (i) precocious onset of pubertal development at a very young age, (ii) hormonal findings compatible with CPP, (iii) demonstration of an isointense tumor in a typical location showing no gadolinium enhancement on MRI and (iv) gelastic seizures, abnormal behavior and mental retardation (8–10). CPP may be associated with hamartoma, glioma, neuroblastoma, tuberculosis meningitis, craniopharyngioma and arachnoid cyst. Hamartoma is one of the most frequently cited causes of CPP (11). MRI is a necessary diagnostic tool for detecting CPP with HH. In the present cases, MRI showed a nonenhancing, stable isointense lesion on T_1-weighted images that was hyperintense or isointense on T_2-weighted images as compared with gray matter. The differential diagnosis includes ganglioglioma, astrocytoma, craniopharyngioma, suprasellar germinoma and lymphoma (2). Histologically, HH usually shows low cell density with irregularly structured groups of multipolar ganglionoid cells and myelinated fibers arranged in small bundles. The histological findings of the present cases were compatible with hamartoma. Immunohistochemical studies showed positive staining for neuron-specific enolase, synaptophysin and neurofilament protein; other LH-RH granules have also been detected by staining of specimens from CPP patients with HH (2).

The mechanism by which HH induces CPP is unknown, but it has been speculated that local pressure, abnormal neuronal connections, surgical lesions, independent endocrine activity or combinations of these factors may play a role (2, 12, 13). Other authors have suggested activation of endogenous LH-RH secretion via astroglial-derived factors as a possible mechanism of CPP (6).

In some cases, HH is associated with gelastic and other types of seizures. Mahachoklertwattana *et al.* reviewed the relationship between HH size and the occurrence of seizures and demonstrated that patients with a hamartoma less than 10 mm in diameter did not have seizures. In contrast, all patients with hamartomas of 25 mm or larger had seizures (14). Valdueza *et al.* proposed classifying HH into four groups (Ia, Ib, IIa and IIb) based on topographical and clinical data. In type II, the HH is large, the mass has a sessile attachment and there is clear distortion of the third ventricle. The mass is partially located within the hypothalamus and the third ventricle. CPP patients with HH may have gelastic and mixed seizures, mental retardation and behavioral abnormalities. In types Ia and Ib, HH is associated with CPP without seizures (2). Debeneix *et al.* demonstrated that small pedunculated HHs were associated with CPP, while large sessile HHs were associated with seizures (15). Arita *et al.* classified HH into two categories, the parahypothalamic and intrahypothalamic types, based on MRI findings; they found that the parahypothalamic type was associated with isolated CPP, whereas the intrahypothalamic type was associated with seizures, developmental delay and CPP (16). Delalande *et al.* proposed classifying HH into four types based on anatomy (17). In the present cases, the HHs were sessile and associated with CPP. The HH was 1.2 × 1.5 cm in the case with gelastic seizures and 2.0 × 2.5 cm in the case with EEG abnormalities but no seizures. The HHs involved the hypothalamus and distorted the third ventricle. They would be categorized as type II according to Valdueza *et al.* (2) and as the intrahypothalamic type according to Arita *et al.* (16), but both cases had CPP, and the second had no seizures. Because the pathomechanisms of the clinical manifestations of HH are still unclear and confusion arises from the vagueness of the criteria for the topology of HH, it was difficult to determine a topology/symptom relationship (16).

HH frequently occurs with a variety of cognitive impairments and behavioral abnormalities (3, 8–10). Berkovic *et al.* showed

that HH cases can manifest progressive intellectual deterioration and aggressive behavior. The behavioral abnormalities might be multifactorial in origin due to psychosocial difficulties, hospitalization, mental retardation, epilepsy or drug effects. Episodes of severe rage, a type of behavioral abnormality, were not associated with seizures and may have been related to the lesion. The finding of cognitive impairment indicates diffuse cortical dysfunction (3).

Treatment with a GnRH analogue improves hormonal laboratory findings and the height prognosis of HH patients with CPP (18, 19). HH is not an indication for surgical resection; however, it may be indicated for patients with intractable seizures that cannot be controlled by anticonvulsants (15, 20, 21). Some authors have reported dramatic improvements in behavior and cognition following HH resection (9, 10). Others have reported that complete HH resection in CPP patients completely cures CPP (22, 23). Furthermore, there are also reports indicating that treatments with a GnRH analogue for HH with CPP decrease tumor size and suppress gelastic seizures; however, the underlying mechanisms were not clarified (24, 25).

Of the two HH cases with CPP presented herein, the first was treated with a γ-knife, surgical removal of the HH, and then GnRH analogue therapy for CPP. This patient's IQ score increased from 66 to 86 after 7 mo of GnRH analogue treatment. He is currently undergoing GnRH analogue treatment again. The second case received partial surgical removal and GnRH analogue treatment. This patient's DQ score before starting GnRH analogue therapy was 86 (CA of 1 yr 6 mo), and after surgical removal of the HH followed by GnRH analogue therapy, his IQ was 116 (CA of 4 yr 8 mo). It appears that GnRH analogue therapy and surgical HH removal improved the DQ/IQ score in this patient, as well as his abnormal movements. GnRH analogue therapy is known to affect hormonal function and suppresses estrogens. Estrogens may have a proconvulsant effect, and treatment with estrogens has been reported to be associated with behavioral changes in animals, including stereotypical recurrent behaviors (26, 27). GnRH analogue therapy has been reported to slightly decrease problematic behavior and improve functioning (28).

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