

Gamma knife radiosurgery for hypothalamic hamartomas in patients with medically intractable epilepsy and precocious puberty

Report of two cases

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✓ Hamartoma of the hypothalamus represents a well-known but rare cause of central precocious puberty and gelastic epilepsy. Due to the delicate site in which the tumor is located, surgery is often unsuccessful and associated with considerable risks. In the two cases presented, gamma knife radiosurgery was applied as a safe and noninvasive alternative to obtain seizure control.

Two patients, a 13-year-old boy and a 6-year-old girl, presented with medically intractable gelastic epilepsy and increasing episodes of secondary generalized seizures. Abnormal behavior and precocious puberty were also evident. Magnetic resonance (MR) imaging revealed hypothalamic hamartomas measuring 13 and 11 mm, respectively. After general anesthesia had been induced in the patients, radiosurgical treatment was performed with margin doses of 12 Gy to 90% and 60% of isodose areas, covering volumes of 700 and 500 mm³, respectively.

After follow-up periods of 54 months in the boy and 36 months in the girl, progressive decrease in both seizure frequency and intensity was noted (Engel outcome scores IIa and IIIa, respectively). Both patients are currently able to attend public school. Follow-up MR imaging has not revealed significant changes in the sizes of the lesions.

Gamma knife radiosurgery can be an effective and safe treatment modality for achieving good seizure control in patients with hypothalamic hamartomas.

KEY WORDS • epilepsy • gelastic seizure • hypothalamic hamartoma • precocious puberty • radiosurgery

HAMARTOMA of the hypothalamus is a rare congenital malformation in which ectopic neuronal tissue originates in the region of the tuber cinereum. In most cases, such lesions are discovered during a workup for precocious puberty (a complex problem of either central or peripheral origin) or for seizures. The typical appearance of this lesion is that of a spherical mass at the midline, usually located below the tuber cinereum and measuring between 0.5 cm and 4 cm, in most cases less than 1.5 cm. Hypothalamic hamartomas may either be pedunculate or sessile.^{26,32} Thus far, the mechanism by which these lesions induce seizures or precocious puberty is not yet fully understood. Seizures occur more often in sessile tumors and may take the form of gelastic epilepsy, characterized by brief episodes of clonic facial grimaces ac-

companied by bubbling or laughing noises. Usually, they first appear during early childhood, occur frequently, and constitute an unfavorable prognostic sign. Often this type of epilepsy is accompanied by progressive mental deterioration.⁸

Since 1934 when the first case of hypothalamic hamartoma was described,¹¹ more than 90 cases have been reported in the literature. Previous treatment modalities included surgical removal of the tumor, which is still controversial because of the peculiarity of the lesion and the fact that surgery may result in hypothalamic dysfunction and damage to the mammillary bodies. Stereotactically guided radiofrequency thermocoagulation was successful in four patients, confirming the feasibility of this treating modality.^{13,18} To date, radiosurgical treatment has been reported in two cases.^{4,20} Radiosurgery was selected for the patients in this report because surgery of these lesions carries considerable risks due to their incorporation within hypothalamic tissue and because the patients' parents insisted on a noninvasive treatment after they had been informed of the therapeutic alternatives.

Abbreviations used in this paper: CT = computerized tomography; EEG = electroencephalography; FSH = follicle-stimulating hormone; GH = growth hormone; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone; LHRH = LH-releasing hormone; MR = magnetic resonance; TSH = thyroid-stimulating hormone.

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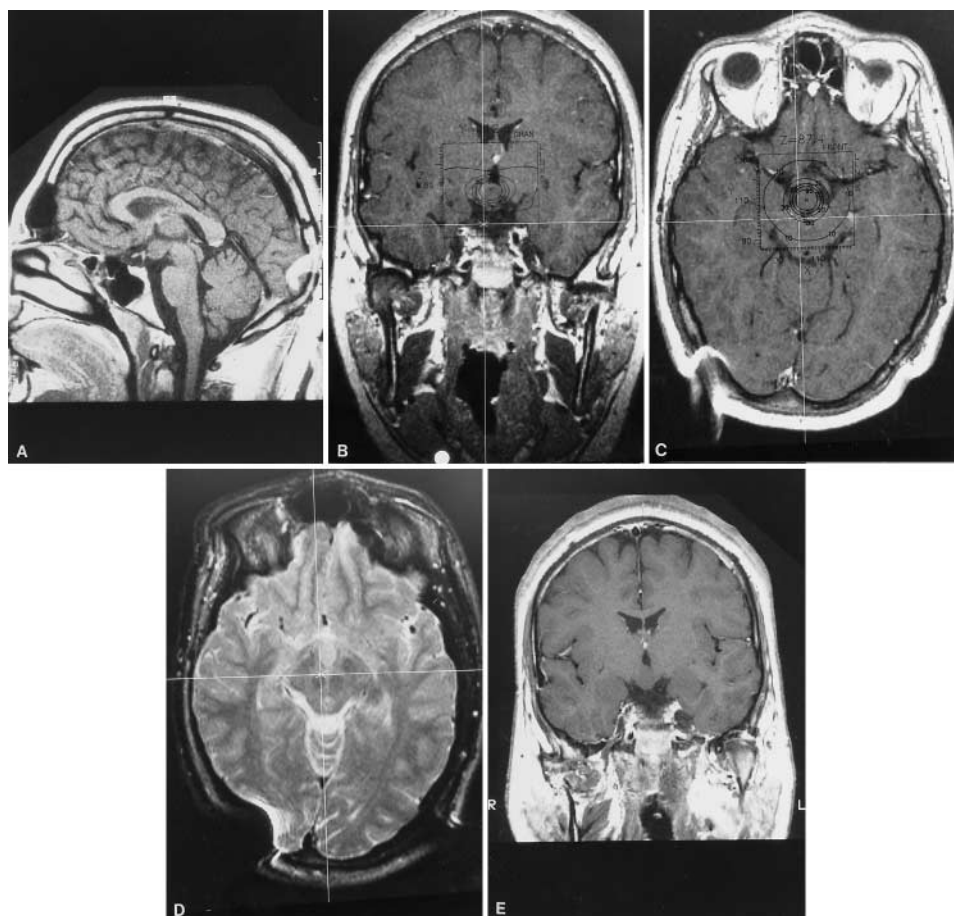


FIG. 1. Case 1. A: Gadolinium-enhanced T₁-weighted sagittal MR image obtained in a 13-year-old boy with a sessile hypothalamic hamartoma measuring 13 mm in diameter. The lesion appears isointense in relation to gray matter before radiosurgery. B and C: Gadolinium-enhanced T₁-weighted coronal (B) and axial (C) MR images obtained for gamma knife planning. D: A T₂-weighted axial MR image obtained for gamma knife planning demonstrating increased signal intensity. E: Gadolinium-enhanced T₁-weighted coronal MR image obtained 50 months after radiosurgery. The tumor remains unchanged in size.

Case Reports

Case 1

History and Examination. This 13-year-old boy was healthy at birth. By the time he was 2 years of age, he exhibited gelastic epilepsy associated with retardation in speech and motor activity. Neurological and EEG findings were inconclusive. Because hearing loss was suspected, the child underwent an otorhinolaryngological examination, the results of which were normal. The child's physical and mental development remained delayed. From the time he reached 6 years of age, the frequency and intensity of the gelastic seizures increased gradually and secondary generalization of seizures occurred. An interictal EEG examination demonstrated slow waves in the right temporal region and an ictal EEG study performed during gelastic seizures showed initially slow waves followed by diffuse depression and spike waves. The results of CT scans were not conclusive. At the age of 8 years, precocious puberty became evident, with levels of serum testosterone (6.1 mIU/ml), LHRH (9.7 mIU/ml), and LH (9.7

mIU/ml) corresponding to levels normally found in adults. Both GH and TSH levels were normal.

Magnetic resonance imaging studies revealed a sessile hypothalamic hamartoma (Fig. 1A); however, the boy's parents were reluctant to agree to any form of surgical intervention. At the age of 10 years, the child presented at our department for the first time with weight and height ranging beyond the 97th percentile. Within the following 3 years, the boy became increasingly socially disabled because of the secondary generalization of seizures, which occurred in excess of 10 times per month and were accompanied by more than 50 gelastic seizures within the same period. Because multiple drug regimens failed to effect seizure control (last medication regimen: carbamazepine 1200 mg and Lamotrigin 200 mg), the patient was no longer able to attend school.

Radiosurgery. In January 1994, at the age of 13 years, the boy underwent gamma knife radiosurgery. The procedure was performed using the Leksell gamma knife (model B; Elekta AB, Stockholm, Sweden) with 201 ⁶⁰Co beams delivering the radiation. After being placed in an

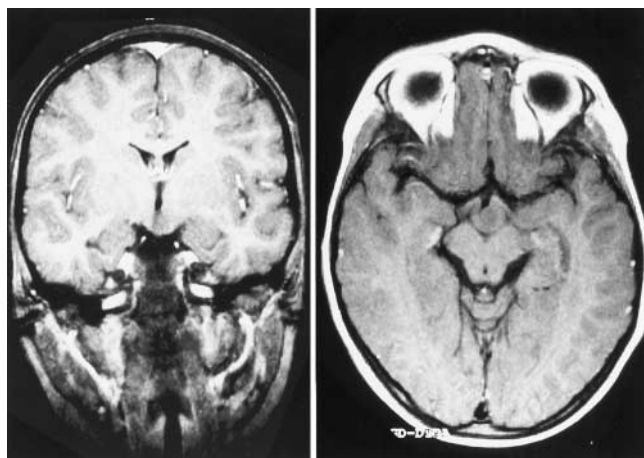


FIG. 2. Case 2. Gadolinium-enhanced T₁-weighted coronal (left) and axial (right) MR images obtained before radiosurgery in a 6-year-old girl with a sessile hypothalamic hamartoma measuring 11 mm in diameter.

image-compatible Leksell stereotactic coordinate frame (Fig. 1B–D), the patient underwent the procedure in a state of general anesthesia. One shot, in which a marginal isodose volume of 12 Gy was delivered to the 90% isodose area, was applied through a 14-mm collimator with a target volume of 700 mm³. The optic tract was exposed to a radiation dose of 6 Gy in a very limited sector.

Posttreatment Course. The patient's postradiosurgical course was uneventful. With a simultaneous improvement in social behavior, his epileptic activity began to decrease after 1 year. Neuroophthalmological examination yielded normal findings. The results of hormonal studies were essentially the same as those obtained before radiosurgery, with adult levels of serum testosterone, LHRH, and LH. According to follow-up MR images, there was no significant change in the size of the lesion (Fig. 1E). After a follow-up period of 54 months, the patient experienced only occasional gelastic seizures (< three per month) and was free from generalized seizures. The patient proved to tolerate antiepileptic medication (900 mg carbamazepine administered daily) well (Engel outcome score IIa).¹² Socially reintegrated, the boy has completed a basic school training. The EEG findings improved, presently demonstrating only occasional slow waves on the right temporal side.

Case 2

History and Examination. This 6-year-old girl reached her developmental goals appropriately until the age of 4 years, when she began to experience gelastic seizures and a precocious puberty, which was noted by her mother. The results of CT scans were inconclusive. An EEG examination revealed slow waves in the patient's left hemisphere; however, there was no epileptic focus to be detected.

Endocrine studies revealed elevated basal serum levels of LH and FSH and an excessive reaction to LHRH. Both GH and TSH levels were normal, as were other laboratory data. The patient's estradiol level (22 pg/ml) was slightly elevated (normal concentration ≤ 15 pg/ml).

Magnetic resonance imaging studies revealed a nonenhancing sessile mass in the hypothalamus (Fig. 2) measuring 1.1 cm in diameter. Following an ineffective treatment attempt in which a long-acting GnRH analog was administered, the patient presented at our department with symptoms of continuing precocious puberty and increasing secondary generalization of the gelastic seizures. Multiple antiepileptic drug regimens were unsuccessful. The gelastic seizures occurred more than 20 times per month with generalized seizures occurring approximately four times within the same period. Interictal EEG demonstrated multifocal and, later, generalized multiple spike-and-slow-wave activities.

Radiosurgery. In December 1995 the girl, then aged 6 years, underwent radiosurgery while in a state of general anesthesia. Via four shots through 8-mm collimators a radiation dose of 12 Gy was delivered to a 60% isodose area covering a volume of 500 mm³.

Posttreatment Course. The patient's postradiosurgical course was uneventful. An initial decrease in epileptic activity was observed after 8 months; by 36 months post-treatment, a worthwhile improvement was evident. At the present time, generalized seizures are exceptionally rare, and gelastic seizures do not occur more than two times per week. This patient is currently taking a daily dose of 600 mg oxcarbazepine. Unfortunately, the girl's parents have not adhered strictly to the prescribed regimen. Until now, the patient's clinical signs have remained unchanged, despite a decrease in both basal and stimulated LH and FSH levels. On MR images the lesion appears unchanged. A neuroophthalmological examination yielded normal results. The girl is currently attending public school.

Discussion

Tuber cinereum is a descriptive name for the region encompassing the small bilateral protuberances of gray matter and the middle hypothalamic nuclei that are located between the infundibular stalk and the large prominent mammillary bodies.⁹

Hamartomas of the hypothalamus are congenital and, thus, do not represent true neoplasms. Developmentally, the tissue displacement probably arises when the ventral aspect of the neuraxis approaches the anterior tip of the end of the notochord during the 5th or 6th week of gestation.⁷ Hypothalamic hamartomas are characterized by their stable site and lack of invasiveness over time. Both CT and MR imaging studies are invaluable in differentiating them from other suprasellar mass lesions in children. Craniopharyngiomas are often cystic, contain calcification, and are rarely located solely at the interpeduncular cistern. They may present a broad variety of appearances on MR images. Optic gliomas are generally hypointense on T₁-weighted images and hyperintense on T₂-weighted images. In many cases, an enlargement of the optic nerves, optic chiasm, or optic tract can be seen. Intracranial germinomas constitute rare lesions that enhance in response to administration of contrast medium. Commonly, precocious puberty is not a typical clinical feature, whereas tumor growth documented by sequential examinations supports the diagnosis of germinoma. Hypothalamic gli-

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TABLE 1
Summary of clinical data obtained since 1990 in patients harboring hypothalamic hamartomas and exhibiting gelastic epilepsy*

Authors & Year	No. of Cases	Age (yrs), Sex	Clinical Presentation	Age (yrs) at SO	Treatment	Size of Tumor	Outcome
Machado, et al., 1991	1	7, F	GE, GTCS, PP, B/MD	<1	TR	2.5 cm	SS
Valdueza, et al., 1994	4	5, M	GE, GTCS, TS, B/MD	<1	PR	2 cm	I, B/MD, I
		6, M	GE, AS, B/MD	<5	TR	2 cm	SS, B/MD, I
		27, F	GE, TS, VI	4	CM	1.5 cm	no change
		10, F	GE, GTCS, B/MD, PP	<5	CM	2 cm	I
Munari, et al., 1995	1	16, F	GE, TS, GTCS	<3	RS	1.8 cm	no change
Kuzniecky, et al., 1997	3	3, F	GE, GTCS, B/MD, PP	<1	RFT	(range in all patients	I, B/MD, no change
		25, F	GE, GTCS, B/MD, PP	<1	RFT	1300–3100 mm ³)	I, B/MD, no change
		30, M	GE, GTCS, B/MD, PP	<1	RFT		SS, B/MD, I
Arita, et al., 1998	1	25, M	GE, GTCS	<1	RS	1 cm	SS w/ medication
Fukuda, et al., 1999	1	15, F	GE, GTCS, sl PP, B/MD	<2	RFT	1 cm	SS
Striano, et al., 1999	4	3, F	GE, B/MD	<1	TR	NR	I
		26, M	GE, GTCS, B/MD	6	TR	NR	sII
		48, M	GE	20	CM	NR	I
		NR, F	GE, GTCS, B/MD	<1	CM	NR	no change
		13, M	GE, GTCS, PP, B/MD	2	RS	1.3 cm	I (seizure & B/MD)
present study	2	6, F	GE, GTCS, PP, B/MD	4	RS	1.1 cm	sII (seizures & B/MD)

* AS = adersive seizures; B/MD = behavior and/or mental disorders; CM = conservative management; GE = gelastic epilepsy; GTCS = secondary generalized tonic-clonic seizures; I = improved; NR = not reported; PP = precocious puberty; PR = partial resection; RFT = radiofrequency thermocoagulation; RS = radiosurgery; sl = slightly; SO = seizure onset; SS = seizures subsided; TR = total resection; TS = temporal seizures; VI = visual impairment.

mas and gangliogliomas appear inhomogeneous and display contrast enhancement.

In MR imaging studies of hypothalamic hamartomas, the mass appears isointense with respect to gray matter and exhibits mostly hyperintense signal characteristics on T₂-weighted images.¹⁵ As a diagnostic tool, MR imaging offers the additional advantage of assessing any associated intracranial abnormalities, such as callosal agenesis, optic malformation, and hemispheric dysgenesis (heterotopias and microgyria).⁷

Valdueza, et al.,³² proposed a classification of hypothalamic hamartomas based on topographical and clinical data obtained in 42 patients. Based on the categories of size, type of attachment, origin, extent of hypothalamic displacement, and common features, four subgroups of these lesions were established. The patients described in this paper meet the criteria of Type IIb (medium-large size, sessile with hypothalamic displacement, and comorbid states of precocious puberty, gelastic epilepsy, and behavioral disorder).

The pathogenesis of precocious puberty remains uncertain. The mean age for onset of puberty is 10 years in girls and 12 years in boys, with a range of approximately 2 years. Precocious puberty is diagnosed when typical signs occur in girls younger than 8 years of age or in boys younger than 9.5 years of age. A central precocious puberty is characterized by pubertal or adult levels of LH, FSH, and estradiol or testosterone, and pubertal or mature responses to GnRH stimulation.

Precocious puberty may arise following a stimulation of the anterior hypothalamus, which is responsible for sexual development, or of the posterior hypothalamus by mechanical interruption of inhibitory pathways to the pituitary gland, which locks the release of gonadotropin-releasing factor from the median eminence. In addition, a

third mechanism in which autonomous production and release of LHRH occurs has been suspected.

In our patients, precocious puberty was not resolved by radiosurgery. However, at the time of treatment, the boy in Case 1 had already reached the age for normal onset of puberty, whereas in Case 2 progression of the girl's symptoms slowed, at least with respect to a decrease in serum levels of LH and FSH. The effects of radiosurgery on seizures were delayed and did not correlate with changes in hormone parameters.

Hypotheses explaining the origin of seizures in patients with hypothalamic hamartomas include: interconnection of the hamartomatous neurons with those of the limbic system, and seizures associated with midline abnormalities or hemispheric malformations.

Gelastc epilepsy is distinguished from epileptic laughter associated with temporal lobe seizures by onset, frequency, and character.^{3,8,14,21,22} The mechanism is unclear, representing either mechanical stimulation of the floor of the third ventricle by the tumor with epileptic discharge from the hypothalamus or some kind of automatism or release phenomenon. Temporal lobe epilepsy can also be associated with laughter. In the cases presented here, a standard EEG examination was not able to detect the epileptic focus. Thus MR imaging studies were used for target localization.

Although epilepsy did not cease completely in these two cases, there was a marked improvement in Case 1 and a worthwhile alleviation of symptoms in Case 2.

Medication, surgery, and radiotherapy have been used as treatment modalities in patients with hypothalamic hamartoma. Long-acting GnRH analogs have been effective in some cases; however, long-term treatment is expensive.

Despite some reports of successful surgical treat-

ment,^{1,19,25,30} surgery for hypothalamic hamartomas has often been disappointing up to recent times.^{2,10,24,28} Although asymptomatic hypothalamic hamartoma would not require treatment, Valdueza, et al.,³² recommend surgery as the therapy of choice in cases of progressive visual impairment and failure of medical treatment (long-acting LHRH analogs).³² The same applies to patients with Type IIb hamartomas, in whom epileptic activity and behavioral abnormalities are usually progressive and difficult to control. By contrast, Humphreys¹⁶ emphasizes the lack of extensive experience with treatment techniques for hypothalamic hamartomas and remains uncertain about the benefit of exploration via open craniotomy.

Because hamartomas are regarded as not being radiosensitive, conventional radiotherapy has rarely been applied.²⁵ However, there have been recent reports of successful stereotactically guided radiofrequency thermocoagulation. Kuzniecky and associates¹⁸ documented three cases of hypothalamic hamartomas with gelastic epilepsy in which lesioning was used; another case was reported by Fukuda, et al.¹³ Seizures ceased according to depth-electrode recordings, which allowed both direct confirmation of the seizure focus and guided placement of the electrodes. In contrast to radiosurgery, tissue samples can be obtained for histological examination. An overview of patients with hypothalamic hamartomas who underwent different treatment modalities in the past decade is presented in Table 1.

There have been various attempts to explain how radiosurgery may have a beneficial effect on epilepsy, but the mechanism remains still uncertain.^{5,27,31} Based on experimental studies, Barcia-Salorio and colleagues⁵ hypothesized that there may be a decrease in gliosis in the focus, which has a direct effect on pathological neurons. In some cases of tumor-induced epilepsy, gamma knife radiosurgery may yield similar results to open surgery, if a low dose of radiation is applied to a relatively large area outside the tumor volume. In our patients, highly vulnerable structures in the hypothalamus had to be preserved. The marginal isodose of 12 Gy applied to the tumor therefore had to be delivered using an isodose configuration with a steep dose decline outside the tumor volume. The optic tract, which can tolerate up to 10 Gy, was exposed to a radiation dose of 6 Gy.^{17,24} The effects on epileptic activity, which were delayed but occurred progressively, support the hypothesis of a long-term structural change affecting the epileptogenic focus. Another case has been recently published by Arita and colleagues⁴ who stated that application of 18 Gy to the 50% isodose area achieved seizure control and, moreover, a complete disappearance of the lesion was noted on MR images 12 months later—a result that has to be regarded as extremely uncommon. By contrast, Munari, et al.,²⁰ reported a case in which stereotactically guided radiosurgery performed using a linear accelerator proved to be ineffective. The authors attributed this unfavorable outcome to an inadequate dose–target relationship.

Irradiation to the brain may give rise to severe side effects, especially in children. Therefore, the option of gamma knife treatment has to be examined carefully. There are some reports about the role of radiosurgery in children.^{6,23} Although there are no long-term follow-up findings available so far, treatment has usually been well

tolerated. Problems comparable to those observed after conventional external-beam radiation therapy have not been noted. Primarily because of the necessity to immobilize the head in a stereotactic frame, children undergoing stereotactically guided radiosurgery frequently require induction of general anesthesia.²⁹

Conclusions

Low doses of radiation (10–20 Gy) have proved effective for the suppression of epileptogenic activity and minimize the risk of complications due to irradiation toxicity. To date, the number of radiosurgically treated cases is still too small for final conclusions to be drawn. This applies especially for children with precocious puberty in whom serum hormone levels did not return to normal range, although an amelioration could be observed. Currently, radiosurgery for epilepsy is still in search of an optimized radiation dose, localization, and target volume. Therefore radiosurgery cannot replace open surgery in general; however, it may be considered an alternative in cases in which foci are located close to functionally important brain areas because of the low risk of side effects.

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