Radiosurgery for hypothalamic hamartomas

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Radiosurgery plays an important role in the treatment of refractory seizures induced by hypothalamic hamartomas (HHs). These lesions, deeply located and surrounded by a delicate vascular and neuronal network, are often associated with catastrophic epilepsy leading to progressive cognitive and behavioral deterioration. Surgical approaches include microsurgical resection, endoscopic resection or disconnection, radiofrequency lesioning, and interstitial brachytherapy. Radiosurgery is an emerging treatment modality for HHs, which provides excellent seizure outcomes and no lasting complications to date. (DOI: 10.3171/FOC/2008/24/5/E9)

KEY WORDS • epilepsy • gelastic seizure • hypothalamic hamartoma • image guidance • stereotactic radiosurgery

Abbreviations used in this paper: EEG = electroencephalographic; HH = hypothalamic hamartoma; MR = magnetic resonance.
Both T2-weighted fast spin echo and neuroimaging of HH

Modern neuroimaging that involves a 1.5-T or, more recently, a 3-T MR imaging unit is an essential modality in the pathophysiological and presurgical evaluation of patients with HH. Both surgical or radiosurgical planning strictly depend on the peculiar anatomical features of each case. The first goal is to establish the size and location of the HH. To plan the best approach to the lesion, it is crucial to evaluate whether the HH is contained within the hypothalamus (a sessile HH) or growing mainly in the third ventricle and extending into the interpeduncular fossa (pedunculated HH). Increased T2-weighted signal intensity relative to gray matter, lack of contrast enhancement, and stable lesion size over time are common MR imaging features of HH. Intra-hypothalamic HHs have a tight spatial relationship to surrounding nuclei and fiber tracts such as the mammillary bodies, the postcommissural fornix, the mammillothalamic tract, the tuber cinereum, the pre- and supraoptic nuclei, the optic chiasm, and the pituitary stalk. These structures can be variably deformed, displaced, or inglobated within the HH (for example, the mammillothalamic tract, rather than being displaced posteriorly, can be found running inside the lesion [Fig. 1]). A common neuroimaging finding involves the posterior displacement of the mammillary bodies, which assume a concave shape, like a crescent, filled by the HH (Fig. 2). The intra-hypothalamic component typically lies in the wall of the third ventricle between the postcommissural fornix anteriorly, the mammillothalamic tract posteriorly, and the mammillary body inferiorly (Figs. 1 and 2). The hypothalamic attachment is often asymmetrical; it has been noted that even small unilateral HHs attached to one side of the hypothalamus are epileptogenic. Both T2-weighted fast spin echo and proton density MR imaging studies are the best modalities for delineating the relation of the HH (typically hyperintense) to the postcommissural fornix and the mammillothalamic tracts, which are markedly hypointense compared with the HH (Fig. 1). Hypothalamic hamartomas growing into the interpeduncular fossa assume a close spatial relationship with the optic chiasm anteriorly and the optic tracts sideways (Fig. 2).

The authors of a recent study performed in 72 patients have extensively analyzed the neuroradiological features of epileptogenic HHs and their relation to nearby structures. All the patients included in this study had medically refractory epilepsy. The onset of seizure manifestation ranged from birth to 16 years of age (median age 3 months). Mean patient age at the time of the last MR imaging examination was 12 years (range 22 months–31 years). Precocious puberty was documented in 28 patients and was associated with larger HH size and contact with the pituitary stalk. Either sessile (Valdueza Type IV lesions) or pedunculated HH could be associated with precocious puberty. The absence of tuberal involvement was associated with normal pubertal development. The size of the HH ranged from 8 to 42 mm (mean 19 ± 8 mm [standard deviation]). The smallest lesions were entirely or predominantly intraventricular, whereas the larger lesions were both intraventricular and interpeduncular. Valdueza Type IIa lesions were found to be the most common epileptogenic lesions. All 72 hamartomas involved the mammillary region of the hypothalamus, and all but 6 encroached onto the tuber cinereum; 16 large lesions (22%) extended rostrally and reached the optic chiasm. No hamartomas increased in size or changed appreciably in appearance during the interval between studies. For the 55 cases in which contrast medium was administered, no enhancement of the lesions was observed. Signal intensity of the HHs was increased (relative to cortical and deep gray matter) on T2-weighted MR images in 67 patients (93%) and was slightly decreased on T1-weighted images in 53 patients (74%). Proton density weighted or fluid-attenuated inversion recovery imaging was performed in 67 cases, 58 (87%) of which exhibited relatively high signal intensity relative to the gray matter. Spectroscopy revealed increased myoinositol levels and...
low N-acetyl aspartate concentration within the HH, suggesting gliosis and neuronal loss.  

Pathophysiology: Intrinsic Epileptogenesis of HHs

Scalp EEG recording in patients with HH-induced seizures is characterized by generalized spike and wave patterns variably associated with generalized tonic or tonic–clonic seizures, drop attacks, and partial seizures. Children may present with EEG features of epileptic encephalopathy resembling those of the Lennox–Gastaut syndrome. Ictal and interictal epileptic abnormalities localized in the temporal and frontal lobes are frequent and lead many epileptologists to believe that gelastic (and other) seizures originate from independent neocortical foci. The hypothesis of an intrinsic epileptogenesis of HH gained impetus after the stereo-EEG demonstration of ictal onsets originating from the hypothalamic lesion, and was further corroborated by subsequent reports showing production of typical gelastic seizures by depth electrode stimulation, ictal SPECT studies demonstrating HH hyperperfusion, and interictal spike source analysis. The epileptogenic activity of HHs has been recently demonstrated at the cellular level: detailed electrophysiological analysis of slices taken from surgical specimens showed the predominance of small GABAergic inhibitory neurons exhibiting an intrinsic “pacemaker-like” behavior.  

The concept that surgical intervention should mainly target the HH was not easy to accept. The path toward acceptance was paved by failed procedures such as temporal or frontal lobectomies, parietal corticectomies, or corpus callosotomies. Even in recent surgical series there are patients who underwent temporal lobectomies or other procedures rather than HH resection and were later referred to a center where the lesion was finally resected. This also reflects the hesitancy of neurosurgeons to operate on a dienephalic lesion stemming from the hypothalamus, which requires a complex procedure followed by a difficult postoperative period in which multiple vascular and metabolic complications (such as diabetes insipidus, SIADH [syndrome of inappropriate antidiuretic hormone], hyperthermia, hyperphagia, and hypothyroidism) may arise.

Substantial seizure improvement following resection, disconnection, or ablation is further proof of the intrinsic epileptogenesis of HHs and the need for a direct approach to produce seizure relief. The degree of seizure control is linked to the extent of the surgical intervention. Incomplete resection, disconnection, or ablation of the HH can be associated with incomplete seizure control, whereas freedom from seizures may be induced by a more aggressive approach. The disappearance of only some seizure types with preservation of others has been described after interstitial brachytherapy; in one study repeated seed implantation induced remission of the residual seizure types as well. On the other hand, reported improved seizure control in 2 patients undergoing radiosurgery, in which there was incomplete coverage of the target to spare the visual pathways. Ictal depth recording showed that different independent epileptogenic zones, associated with peculiar semiological features and intermixed with inactive regions, can be present inside the HH. These observations support the role of focal regions within the HH that are responsible for the origination or propagation of seizures. The ability of an HH to induce generalized seizures likely flows through the mammillothalamic tract linking the mamillary bodies with the anterior thalamic nuclei. The mammillary bodies are tightly connected to epileptogenic HH, while the anterior thalamic nuclei play a crucial role in the genesis of generalized seizures. There is considerable experimental evidence that interruption of the mammillothalamic tract, high-frequency stimulation of the mammillary bodies, or ablation of the anterior thalamic nuclei prevents the generation of generalized seizures. Stereotactic lesioning of 1 mammillothalamic tract induced remission of generalized seizures in a patient with HH.

Surgical Procedures: Resection, Disconnection, and Radiofrequency Ablation

Surgical treatment of HHs for precocious puberty was reported by Northfield and Russell in 1967. The first report of HH resection followed by favorable seizure outcome was published by Paillas et al. in 1969. The feasibility of HH surgery and the demonstration that seizures could be favorably affected was not sufficient, at the time, to convince surgeons to focus treatment of epileptogenic HH on the removal or disconnection of the lesion: this approach, instead, had to wait ~ 30 years. Following the increasing use of epilepsy surgery aimed at mesial temporal or neocortical resection, as well as the presence of localizing EEG activity mainly pointing to temporal or, less often, frontal lobes, patients with HHs were preferentially treated by temporal or frontal lobectomy. The work performed by Munari and associates, who demonstrated the intrinsic epileptogenesis of the HH and localized ictal onsets within the lesion by using stereotactic depth electrodes, was instrumental in directing the efforts of epilepsy surgery teams to the excision of the HHs.

A variety of routes and approaches has been devised to treat HHs, with the transcallosal–transforniceal approach being the most favored. This route provides excellent exposure of intraventricular hamartomas. Resection is an excellent option in cases of large pedunculated HH: the lesser the hypothalamic attachment, the lower the chance to develop metabolic complications. Other approaches allowing partial or total resection or disconnection include the subfrontal transcallosal terminalis, the ptetional transsylvian, and the subtemporal. Endoscopic disconnection can be performed as well. Radiofrequency ablation has also been described. Surgical morbidity is limited overall, especially considering the challenging neural and vascular anatomy surrounding the HH, but includes thalamocapsular infarcts with resulting hemiparesis or hemiplegia, oculomotor palsy, visual field deficits, short-term memory deterioration, hyperphagia, hypothyroidism, and diabetes insipidus. Complete seizure freedom is difficult to achieve, but in most cases remarkable long-term improvements have been reported with near-total resolution of disabling seizure types and enhanced cognitive and psychosocial abilities. Seizure improvements are immediate while cognitive and behavioral improvements tend to accrue over a period of 3–6 months. The main limitation of surgery lies in the inability to completely resect intrahypo-
thalamic lesions without causing serious neurometabolic injury. Compared with small sessile lesions (Valdueza Types I–III), pedunculated and large sessile HHs (Valdueza Type IV) facilitate an open microsurgical resection. Leaving a residual is quite often associated with seizure recurrence and requires further intervention (S. Striano and G. Coppola, personal communication, 2007). If faced with recurrent seizures after hamartoma resection, one may attempt to expand the resection. Radiosurgery is being increasingly used to treat residual HH and recurrent seizures.

**Interstitial Brachytherapy**

Ostertag and coworkers\textsuperscript{46–47} have reported the stereotactic implantation of temporary radioactive I\textsuperscript{125} seeds into the HH to obtain seizure control. It is a minimally invasive approach delivering low-energy gamma-radiation (range 27–35 kV) at a low-dose rate (~ 10 cG/hour). The stereotactically implanted seed delivers the radiation from the center of the lesion outward, with minimal radiation delivered to the surrounding brain. This treatment was initially described in a report including 7 patients harboring 8- to 11-mm–diameter unilateral mesial intrahypothalamic lesions (Valdueza Type I).\textsuperscript{46} Stereotactic placement of the I\textsuperscript{125} seed was performed successfully in 5 patients. Eccentric seed placement was detected in 1 patient. Due to the coarseness of the hamartoma, the seed could not be inserted in 1 patient and the procedure was aborted. Once the patients received a local anesthetic, the seeds were removed from the hamartomas after a mean interval of 24 days. Seizure freedom was achieved in 2 patients. In 2 more patients, only auroras have persisted, and the other patients had some improvement of seizure frequency. The effect of interstitial radiosurgery was fully established within the first 2 months of seed implantation. Three patients with poor improvement underwent seed reimplantation, with improved seizure control in 2. No surgical complications were described. A recent report including a larger number of patients\textsuperscript{48} has confirmed these preliminary results,\textsuperscript{47} with 53% of patients achieving significant improvement in seizure frequency (Engel Class I or II outcome). Hyperphagia with persistent weight gain (up to 20 kg) was noted in 3 patients. There were no other neurological, neuropsychological, or neuropsychiatric side effects. Dedicated neuropsychological testing showed no short-term negative side effects.\textsuperscript{48} Overall, stereotactic brachytherapy appears to be safe and effective but remains an invasive procedure requiring a bur hole and parenchymal penetration. The insertion of the seed can be difficult when the lesion is hard. In cases of eccentric placement the dose distribution may be unfavorable. Also, dose distributions are not as conformal as those achieved by radiosurgery.

**Stereotactic Radiosurgery**

Radiosurgery is an attractive way to treat HH, as shown by the increasing number of reports and patients treated during the last 8 years.\textsuperscript{2,3,8,39–42,46,51–52} Most of these patients harbored small sessile lesions (Valdueza Types I–III), but larger sessile lesions (Type IV) can be safely treated as well. There is good concordance between published outcomes of HH radiosurgery and our personal experience. A good seizure outcome, with total or near-total seizure freedom, can be obtained noninvasively using either high or low doses without irreversible neurological complications.

The eligibility of patients for radiosurgical treatment of intracranial lesions depends mainly on the combination of anatomical and dosimetric factors, such as the volume of the lesion, the presence of nearby radiosensitive structures, and the dose required to achieve the therapeutic goal. The treatment goal of radiosurgery for HH is to deliver doses high enough to affect epileptogenesis without exceeding the tolerance of nearby critical structures. Modern radiosurgical devices such as the Gamma Knife (Elekta AG), CyberKnife (Accuray Inc.), and Novalis (BrainLab AG) can deliver conformal high-dose radiation with steep gradients providing an excellent chance to achieve seizure freedom without hypothalamic or cranial nerve damage. Frameless devices can deliver staged treatment (that is, treatment in >1 radiosurgery session), which can further reduce toxicity when treating large lesions. Radiosurgery is the most accurate image-guided procedure currently available, providing submillimetric accuracy (a target well beyond the current capabilities of image guidance systems used for conventional surgical procedures). Accurate image-guided ablation is an important advantage of radiosurgery; it allows treatment of the entire lesion as visible on neuroimaging studies, including the intrahypothalamic component, which is often spared in open surgery.

Achievement of seizure freedom following radiosurgery is strictly related to the dose delivered: Régis et al. observed that the patients receiving a peripheral dose of 18 Gy (4 patients) delivered from \textsuperscript{60}Co sources (that is, the Gamma Knife) all became seizure free.\textsuperscript{39} To deliver similar doses without causing injury to radiosensitive structures nearby (optic chiasm, optic tracts, pituitary stalk, fornices, mammillary bodies, mamillothalamic bundle, hypothalamic nuclei), dedicated imaging and careful treatment planning achieving conformal and very tight dose distributions are essential. Most of the epileptogenic HHs are small intrahypothalamic or medium-sized sessile intraventricular/interpeduncular lesions (Valdueza Types I–III). The authors of the largest HH series reported a mean lesion size of 19 mm.\textsuperscript{15} Radiosurgical treatment of lesions < 30 mm can be accomplished with steep dose gradients around the target and a consequent low risk of complications. In most patients Engel Class I or II outcomes are seen after radiosurgery.\textsuperscript{42} No serious temporary or permanent complications such as metabolic disorders, hemiparesis, cranial nerve deficits, short-term memory deficits, or radiation-induced edema have been reported. Temporary worsening of seizures can be seen as early as 2 months after the procedure, followed by progressive resolution; this outcome is associated with the delivery of high doses (> 16 Gy).

**Clinical Outcomes of Radiosurgery for HHs**

Successful radiosurgical treatment of epileptogenic HHs was first reported in 1998 by Arita and colleagues.\textsuperscript{4} A nonenhancing and nonprogressive spherical mass, ~ 10 mm in diameter, located on the patient’s right side at the floor of the third ventricle, was treated using the Gamma Knife, which delivered a marginal dose of 18 Gy. Ra-
Radiosurgery induced a temporary increase in the frequency of the seizures followed by a progressive reduction and resolution. Follow-up MR imaging after 12 months demonstrated complete disappearance of the lesion, a finding not replicated in subsequent reports.

On the basis of this experience a prospective multicenter study was conducted, leading to a preliminary report on a cohort of 10 patients with HHs and medically refractory epilepsy. The mean marginal dose (prescribed to the 50% isodose line in most cases) was 15.5 Gy (range, 12–20 Gy). The median maximal diameter of the HHs was 13.5 mm (range 8–22 mm). The median volume of the marginal isodose was 646.7 mm³ (range 134–2674.8 mm³, mean 889.4 mm³). A maximum dose of 10 Gy was allowed to the optic pathways, requiring undercoverage of the lesions in some cases. The proximity of the lesion to the optic tract and chiasm and the poor delineation of the upper part of the lesion, which was often indistinguishable from the surrounding hypothalamus, were reported to be the main challenges during treatment planning.

All patients exhibited improved control of seizures following radiosurgery. Four patients were seizure free, 1 experienced rare nocturnal seizures, 1 experienced some rare partial seizures but no further generalized attacks, and 2 had reductions in the frequency of seizures but persistence of some rare generalized seizures. Two patients experienced unsatisfactory seizure control after the first radiosurgery procedure and became seizure free after a second treatment. A clear correlation between efficacy and dose was observed; the marginal dose was > 17 Gy in all patients in whom seizure freedom was achieved (median prescribed dose 18.6 Gy) and < 13 Gy for all patients who experienced incomplete seizure control (median prescribed dose 12 Gy). No side effects were reported, except for poikilothermia in 1 patient. Two patients experienced substantial behavioral improvements allowing them to return to school. Precocious puberty, present in 3 patients, was not reversed by the treatment. Follow-up MR imaging showed no perilesional edema and shrinkage of the lesion in 2 patients while no change of size was detected in the others.

This preliminary report has recently been updated by Régis and associates, who have now treated > 60 patients. Seizure freedom (Engel Class I) and persistence of rare nondisabling seizures was found in ~ 40 and 20%, respectively, of the 27 patients with follow-up longer than 3 years. These patients experienced a dramatic improvement of sleep quality, behavior, and learning performance at school. No permanent neurological complications have thus far been reported.

The presence of a dose effect, with reduced efficacy at lower doses, was confirmed in other small clinical series. Unger and coworkers delivered marginal doses of 12–14 Gy. After a follow-up period of 12–68 months, a decrease in seizure frequency and intensity was noted, but no patient became seizure free. Barajas and coworkers reported substantial improvement in seizure control following treatment in 3 patients receiving 12.5, 14 and 15 Gy. Tonic–clonic seizures disappeared completely after 8–12 months, whereas gelastic seizures disappeared almost completely in 2 patients. Dunoyer et al. treated 2 young patients, 4 and 5 years of age, with 11- and 14-Gy doses. The latter patient became seizure free, whereas the former experienced > 90% reduction of seizures.

Overall, it appears that doses in the range of 12–14 Gy may result in relief from seizures, but the degree of amelioration is variable. Early treatment may be associated with more favorable outcomes and could allow the use of lower doses. Delivery of high doses is not uniformly associated with excellent seizure outcomes: in a small group of 4 patients with a long history of symptoms (range 4–28 years), only modest improvements were achieved after the delivery of 17.5 Gy.

In the aforementioned reviews the authors described outcomes after treatment with the Gamma Knife, which delivers gamma rays originating from ⁶⁰Co sources. Linear accelerator–based radiosurgery has proven to be as effective as Gamma Knife. Three patients underwent Novalis radiosurgery in which 6-MV photon beams were delivered (15–18 Gy prescribed to the 90% isodose line). Two patients became seizure free after 7 and 9 months, and 1 patient has rare seizures. We have recently treated 2 patients using the CyberKnife, a frameless radiosurgical device with a robotic 6-MV linear accelerator. About 1 year after the delivery of 16 Gy prescribed to the 80% isodose, a 6-year-old patient presenting with catastrophic epilepsy now has rare seizures while the other (a 22-year-old woman with a long history of seizures) has experienced a modest improvement. Both patients harbored intraventricular (Valdueza Type III) lesions.

Conclusions

Radiosurgery is a safe and effective treatment for HHs. Distinct from other surgical treatments, it is noninvasive and virtually free of major complications, but seizure amelioration requires a several-month interval after radiosurgery to develop. Considering the small size of most HHs, radiosurgery may be investigated as a first-line treatment for these lesions when catastrophic epilepsy with progressive neurobehavioral deterioration or malignant epileptic features, such as frequent generalized seizures and drop attacks, are present.

References


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