Gamma Knife surgery for hypothalamic hamartomas causing refractory epilepsy: preliminary results from a prospective observational study

Clinical article

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_Hypothesis._ Hypothalamic hamartomas (HHs) are congenital lesions typically presenting with medically refractory epilepsy. Open or endoscopic surgical procedures to remove or disconnect the hamartoma have been reported to be effective but are associated with significant morbidity. The authors of studies on Gamma Knife surgery for HHs have reported an encouraging rate of epilepsy resolution with minimal side effects. At the Centre Hospitalier Universitaire de Sherbrooke, the authors have undertaken a prospective observational study of the outcomes of patients who underwent radiosurgery for HHs.

_Meetods._ Patients were included in the study if they had an HH, refractory epilepsy, and no other suspected seizure focus. After radiosurgery, seizure status was assessed every 3 months and reported using the Engel Classification. Quality of life evaluation was performed annually using a standardized questionnaire, and neuropsychological evaluation was performed after 2 years.

_Results._ Nine patients were included in the study. They ranged in age from 12 to 57 years. Epilepsy began in infancy in all cases and was refractory to standard antiepileptic drugs. The patients received an average of 2 antiepileptic drugs before undergoing radiosurgery. Using the Régis Classification, 6 patients had smaller hamartomas (Grade I–III) and underwent treatment of the entire lesion, using a margin dose of 14–20 Gy. Treatment volume ranged from 0.3 to 1.0 ml. Three patients had larger lesions (Grade IV–VI) for which a radiosurgical disconnection was attempted, targeting the area of attachment to the hypothalamus. For those patients, the margin dose was 15 or 16 Gy, with treatment volume ranging from 0.8 to 1.8 ml. In all patients, the radiation dose received by the optic pathways was kept below 10 Gy. Disconnection led to no improvement in epilepsy (Engel Class IV). Four patients in whom the entire lesion was treated were now seizure free (Engel Class I), with another having only rare seizures (Engel Class II). Quality of life and verbal memory were improved in those patients with more than 3 years of follow-up. No adverse event occurred after radiosurgery.

_Conclusions._ Radiosurgery safely and effectively controlled the epileptic disorder in patients with HHs when the entire lesion could be targeted. Radiosurgical disconnection is ineffective and cannot be recommended. (DOI: 10.3171/2010.8.GKS101059)

**Key Words**
- Gamma Knife surgery
- hypothalamic hamartomas
- epilepsy
- quality of life
- radiosurgery

_Hypothesis._ Hypothalamic hamartomas are congenital lesions that usually manifest clinically either as precocious puberty or chronic epilepsy, based on their morphological characteristics. Epilepsy associated with HH usually begins in infancy, manifesting with gelastic seizures. Over time, patients develop multiple seizure types that are typically refractory to treatment with common AEDs, leading eventually to variable cognitive decline. Psychiatric and behavioral comorbidities frequently become part of the clinical picture. It is increasingly recognized that prompt surgical therapy is required in patients in whom HH does not respond to medical therapy to prevent the development of irreversible complications and to ensure normal cognitive development.

Various surgical procedures have been attempted to deal with these intrinsically epileptogenic lesions. Open resection, using the ptorial or transcalsosal approach, has been reported to lead to immediate complete seizure freedom. However, because HHs are deeply embedded

**Abbreviations used in this paper:** AED = antiepileptic drug; GKS = Gamma Knife surgery; HH = hypothalamic hamartoma; QOL = quality of life; QOLIE = QOL in epilepsy.
in the hypothalamic region, direct resection can lead to significant morbidity.\textsuperscript{1,9} To minimize surgical risks, minimally invasive procedures, such as stereotactic GKS, endoscopic resection, and stereotactic radiofrequency thermocoagulation have been proposed as surgical alternatives.\textsuperscript{1,9}

The antiepileptic effect of stereotactic radiosurgery is well demonstrated in the literature, with preclinical and clinical reports of seizure resolution after a latency period which usually lasts a few months.\textsuperscript{5,11,14} The largest reported experience of GKS for HH causing epilepsy is the multiinstitutional study led by the Marseille group. In their latest paper, they reported treating 60 patients, with 27 having more than 3 years of follow-up after GKS.\textsuperscript{18} Ten (37\%) of 27 patients had become seizure free and 6 more (22.2\%) had significant seizure reduction, for a total of 60\% with good clinical outcome. No permanent morbidity occurred after treatment. In addition to the Marseille experience, other groups have reported on limited numbers of patients with variable seizure outcome but minimal side effects.\textsuperscript{2,13,21}

At the Centre Hospitalier Universitaire de Sherbrooke, we have undertaken a prospective observational study of the outcomes of patients who underwent radiosurgery for HH. In addition to seizure evolution, we aimed to assess the effects of GKS on quality of life and neurocognition. We report our preliminary experience to date.

**Methods**

This study was approved by the institutional research ethics committee. Patients were eligible if they had epilepsy that remained refractory to adequate AED therapy, with demonstration on MR imaging of a lesion compatible with an HH. Patients were excluded if they had any other potential seizure focus that was identified on comprehensive presurgical epilepsy workup.
Baseline information included a detailed monthly seizure count, AED usage, age at seizure onset, type of seizures, and prior surgical intervention. Before GKS, patients were asked to fill out a standardized QOL questionnaire validated for epilepsy patients (QOLIE-89), and a baseline neuropsychology evaluation was performed.

Radiosurgery was performed under local anesthesia with conscious sedation for older patients, and after induction of general anesthesia in patients younger than 12 years of age or in cases of severe mental retardation. A Leksell G stereotactic frame was applied, and volumetric Gd-enhanced T1-weighted MPRAGE (magnetization prepared rapid acquisition gradient echo) and T2-weighted MR images were acquired for treatment planning. All treatments were performed using a Leksell Gamma Knife 4C (Elekta Instruments AB) with Leksell GammaPlan software for dose planning. The dosimetry and treatment were tailored to the hamartoma morphology, based on the classification proposed by Régis and colleagues. The goal was to treat the entire hamartoma using a margin dose of up to 20 Gy if possible (Fig. 1). In cases of larger HHs (Grade IV or VI), to limit the radiation dose and volume, only a radiosurgical disconnection was attempted, targeting the area of attachment of the hamartoma to the hypothalamus (Fig. 2). In all cases, the plan was designed to keep the radiation dose to the optic pathways to less than 10 Gy.

After radiosurgery, evaluation (seizure counts and neurological examination) was performed every 3 months by the patient’s referring neurologist. Seizure outcome was graded according to the Engel Classification. Patients were asked to complete the QOLIE-89 questionnaire once every year, and repeated neuropsychology evaluation was conducted 2 years after radiosurgery.

**Results**

Nine patients have been included in the study to date,
with ages ranging from 12 to 57 years at time of GKS. Six patients were using 2 different AEDs at the time of radiosurgery, and 3 patients received 3 drugs. In all cases multiple drug trials had failed.

In 6 patients with smaller hamartomas (Grade I–III), the entire HH was targeted with a margin dose ranging from 14 to 20 Gy delivered at the 50% isodose line; treatment volume ranged from 0.3 to 1.0 ml; and follow-up ranged from 6 to 42 months. To date, 4 (66.7%) of these 6 patients have become seizure free (Engel Class I) since GKS, but AEDs were reduced in only 1 patient. One patient now only suffers rare seizures (Engel Class II) and the other has not seen any significant change (Engel Class IV), both after 6 months since radiosurgery. No clinical side effects have been recorded since GKS. On follow-up MR imaging, we noted a 50% decrease in hamartoma size after 3 years in 1 patient (Fig. 3), and asymptomatic T2 signal changes around the hamartoma with new contrast intake on T1-weighted images 6 months after GKS in another patient (Fig. 4). There was no change on MR imaging in the other 4 patients. Two patients have reached sufficient follow-up to undergo QOL and neuropsychology evaluation. The first has now reached the 42-month mark since undergoing GKS. His QOLIE-89 score has improved from 75 to 84, but he unfortunately declined to undergo repeat neuropsychology evaluation. The second patient has reached the 38-month follow-up since GKS. His QOLIE-89 score showed major improvement (from 51 to 98), and his verbal memory has significantly improved on neuropsychological assessment. Evaluation will be performed later in the remaining 4 patients.

For three patients with large or giant HHs (Grade IV or VI), only a radiosurgical disconnection was attempted. A margin dose of 15 or 16 Gy delivered at the 50% isodose line was delivered to the area of attachment to the hypothalamus. The treatment volume ranged from 0.8 to 1.8 ml. The mean follow-up duration in this group has exceeded 3 years (range 36–56 months). None of these patients had any worthwhile seizure reduction (all Engel Class IV) after disconnection. One of the patients also had severe mental retardation, and the hamartoma was part of multiple brain malformations, so neuropsychological and QOL assessments were impossible to begin with. For the other 2 patients, no changes were noted in neuropsychology or QOL after GKS. One of those patients underwent repeated GKS 50 months after the first procedure, with almost complete coverage of the hamartoma by the 50% isodose line (16-Gy margin dose). To date, 6 months after repeated GKS, he continues to have a 50% decrease in seizure frequency (Engel Class III).

Table 1 provides more detailed information about the 9 patients.

**Discussion**

Hypothalamic hamartomas are benign nonneoplastic lesions that often cause a seizure disorder, which if left untreated can lead to a severe epileptic encephalopathy. Medical therapy with AEDs is usually ineffective to control seizures. In recent years, gamma knife stereotactic radiosurgery has emerged as a minimally invasive treatment modality for HH patients. So far, the radiosurgical...
TABLE 1: Summary of characteristics and outcomes after radiosurgery*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex, Régis Grade at Seizure Onset</th>
<th>Seizure Types</th>
<th>AEDs</th>
<th>Follow-Up (mos)</th>
<th>Margin/Max Dose (Gy)</th>
<th>Volume (ml)</th>
<th>Imaging Evolution</th>
<th>Final Engel Class</th>
<th>QOLIE-89 Overall Score</th>
<th>Neuropsychological Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>53, M IV 5 gelastic, CPS CBZ, LTG</td>
<td>56</td>
<td>15/30</td>
<td>0.8 (partial coverage)†</td>
<td>no change</td>
<td>IIIa (after repeat GKS)</td>
<td>no improvement</td>
<td>no change</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>18, M III 7 gelastic, CPS LEV, CBZ</td>
<td>42</td>
<td>14/28</td>
<td>1.0</td>
<td>no change</td>
<td>Id (receiving AEDs)</td>
<td>improvement from 75 to 84</td>
<td>refused by patient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>23, F VI 1 clonic LTG, CZP</td>
<td>42</td>
<td>16/32</td>
<td>1.8 (partial coverage)†</td>
<td>no change</td>
<td>IVb</td>
<td>no improvement</td>
<td>no change</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>39, M I 2 gelastic, CPS, sec generalized OXC, PHT, VPA</td>
<td>38</td>
<td>16/32</td>
<td>0.5</td>
<td>50% reduction in size</td>
<td>Ia (reduced AEDs)</td>
<td>improved from 51 to 98</td>
<td>improved verbal memory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>12, F VI 6 tonic, sec generalized VPA, LEV</td>
<td>36</td>
<td>16/32</td>
<td>1.1 (partial coverage)†</td>
<td>no change</td>
<td>IVa</td>
<td>impossible (severe mental retardation)</td>
<td>not done</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>18, M II–III 6 gelastic, CPS CBZ, CLB</td>
<td>14</td>
<td>18/36</td>
<td>0.6</td>
<td>no change</td>
<td>Ia (same AEDs)</td>
<td>to be done</td>
<td>to be done</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>37, F II 7 gelastic CPS OXC, TPM, CBZ</td>
<td>6</td>
<td>20/40</td>
<td>0.3</td>
<td>no change</td>
<td>IVb</td>
<td>to be done</td>
<td>to be done</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>14, F I–II 8 gelastic CZP, CBZ</td>
<td>6</td>
<td>20/40</td>
<td>0.4</td>
<td>contrast uptake w/ T2 changes around</td>
<td>Ia (same AEDs)</td>
<td>to be done</td>
<td>to be done</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>54, M II 4 SPS, CPS CBZ, LEV, CBZ</td>
<td>6</td>
<td>20/40</td>
<td>0.5</td>
<td>not done yet</td>
<td>IIb (same AEDs)</td>
<td>to be done</td>
<td>to be done</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* CBZ = carbamazepine; CLB = clobazam; CPS = complex partial seizures; CZP = clonazepam; LEV = levetiracetam; LTG = lamotrigine; OXC = oxcarbazepine; PHT = phenytoin; sec = secondary; SPS = simple partial seizures; TPM = topiramate; VPA = valproic acid.
† Patients in whom an attempted radiosurgical disconnection was performed.
literature compares favorably with published surgical results, with similar seizure control rates, but generally lower morbidity. Although seizure control rates of more than 50% have been reported after direct resection of the hamartoma, the morbidity associated with the approaches used is not negligible. Disabling strokes and cranial nerve paresis can occur when using the pterional approach, and the transcallosal approach can lead to short-term memory disturbance in up to 50% of patients, with weight gain and endocrine deficiency occurring frequently. Endoscopic resection or disconnection has been proposed as an alternative to open resection. Rekate et al. reported on their early experience in 44 patients. Complete removal was achieved in 14 patients, 13 of whom became seizure free. Complications occurred in 11 patients (25%), including short-term memory loss in 6 patients, weight gain in 5, and hemiparesis in 1. However, only 3 patients (6.8%) had persistent deficits at 3 months. Nevertheless, direct open surgical or endoscopic procedures have the advantage of providing immediate seizure control when successful. As such, they remain valuable for patients with severe debilitation from their seizure disorder who might not have the luxury of being able to wait for the delayed action of radiosurgery.

Stereotactic radiofrequency thermocoagulation represents another surgical option for seizure control in patients with HH. Kameyama and associates recently reported the outcomes in a cohort of 25 HH patients in whom radiofrequency thermocoagulation was used. A total of 31 procedures were performed, and gelastic seizures resolved in 23 patients (92%), with 19 patients (76%) becoming totally seizure free in the immediate postoperative period. Only transient complications occurred; there was no permanent morbidity.

The largest published GKS experience comes from the Marseille group. Régis et al. recently reported outcomes in 27 (of 60 treated) patients who reached 3 years of follow-up after radiosurgery. The median dose to the margin was 17 Gy (range 13–26 Gy). Good seizure outcome was attained in 59.2% of patients (37% seizure free, 22.2% with significant seizure reduction). Nine patients (33%) reported a dramatic behavior improvement associated with seizure control, and all but 1 patient had some improvement in cognition and behavior. Undesirable effects manifested in the form of transient poikilothermia in 3 patients (11%), and a transient increase in seizures in 4 patients (14.8%). No permanent complication was seen. Multiple smaller retrospective series have been published, with varying outcomes. Mathieu et al. reported on 4 patients treated using margin doses of 16–20 Gy. Two patients had Engel Class II outcome, one Engel III, and one Engel IV. No side effects were seen. Barajas et al. presented 3 patients who had GKS for HH. Margin doses of 12.5 to 15 Gy were used. All 3 patients had improvement in seizure frequency, behavior, and cognition, without adverse events.

In our study, we have confirmed the clinical efficacy and safety of GKS to control seizures and improve cognition and behavior in patients with HHs. No patient suffered any complications after the procedure. All but 1 patient (83.3%) with a small HH in whom the lesion could be completely covered by the prescription isodose had significantly improved seizure control (4 patients with Engel Class I results and 1 with Engel Class II to date). The patient who did not improve is now only 6 months into the follow-up period since radiosurgery, so no judgment on the efficacy can be drawn yet. It is well known that the antiepileptic effect of GKS may occur after a delay of many months to 3 years. For patients with sufficient follow-up, the improvement in epilepsy has translated to significant gain in their QOL and neuropsychology. However, because of limited QOL and neuropsychological follow-up, no firm conclusive implications can be drawn so far. Contrary to what has been suggested by other preclinical and clinical studies, we did not observe any impact of the treatment dose on seizure outcome, as one patient became seizure free after being treated with a margin dose of 14 Gy. However, whenever safely possible, we still try to give a margin dose as high as 20 Gy, because of evidence of increased efficacy associated with higher doses. Based on our results, it seems that radiosurgical disconnection by incomplete coverage of the hamartoma is ineffective. None of our patients treated with this strategy have shown any improvement in epilepsy, cognition, or behavioral status. As such, those patients with larger hamartomas should be treated by alternative means, possibly partial resection, which could be followed by GKS if the residual lesion volume safely allows it. Based on our results and results published in the literature, the ideal HH candidates for radiosurgery will have small-volume hamartomas (Régis Class I–III) causing a chronic seizure disorder without catastrophic neuropsychological deterioration. As such, the expected delay of action of radiosurgery will not have a detrimental effect on the patients.

Conclusions

Radiosurgery is safe and effective to control the epileptic disorder in patients with HH when the entire lesion can be targeted. Radiosurgical disconnection is ineffective and cannot be recommended as initial therapeutic strategy. A longer follow-up duration will be required to assess the real impact of GKS on the QOL and neuropsychology of treated patients.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Deacon, Pinard. Acquisition of data: Mathieu. Analysis and interpretation of data: Mathieu. Drafting the article: Mathieu. Critically revising the article: Deacon. Reviewed final version of the manuscript and approved it for submission: all authors. Administrative/technical/material support: Kenny, Duval. Study supervision: Mathieu, Deacon.

References

Gamma Knife surgery for hypothalamic hamartomas and epilepsy


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