Treatment Options for Gelastic Epilepsy Due to Hypothalamic Hamartoma: Interstitial Radiosurgery
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Surgical treatment of hypothalamic hamartomas (HHs) as the underlying etiology of gelastic epilepsy is associated with a high risk of complications because of the close vicinity of adjacent structures such as the optic tracts and mammillary bodies. Treatment with interstitial radiosurgery uses stereotactically implanted 125I seeds emitting gamma radiation from the center of the lesion, with a steep spatial gradient, over a period of about 3 weeks. This form of HH therapy offers particular advantages regarding the risk for major side effects. In a series of 15 children and adolescents treated in Freiburg, Germany, 53% of patients achieved significant improvement in seizure frequency (Engel class I or II outcome). Transient side effects were related to the development of local edema, resulting in headache and mental slowing. A persistent weight gain was noted in 3 patients, which was severe in 1 (20 kg). There were no other neurologic, neuropsychologic, or neuropsychiatric side effects, which compares favorably with most surgical series.

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G elastic epilepsy caused by hypothalamic hamartomas (HHs) has come into the focus of interest because of both improved abilities to diagnose this epilepsy syndrome based on high-resolution magnetic resonance imaging (MRI) and reports of several groups showing improved treatment outcomes by a variety of newly developed methods, including new resective strategies, disconnective methods, gamma knife or linear accelerator (LINAC) radiosurgery, and stereotactic interstitial radiosurgery. All of these approaches have proven that the severe epileptic encephalopathy can be relieved in a significant percentage of patients, with major beneficial effects on seizure frequency and severity, and cognitive and behavioral problems.

This report focuses on interstitial radiosurgery performed in close collaboration between the Epilepsy Centre and the Department of Stereotactic Radiosurgery at the University Hospital Freiburg, Germany. The methodology of stereotactic seed implantation and the principle of brachytherapy are described. Outcome results and tolerability in a subgroup of 15 children and adolescents with HH and refractory epilepsy are reported. Interstitial radiosurgery is also discussed in the context of alternative treatment strategies reported recently, regarding efficacy, tolerability, and applicability.

Interstitial Radiosurgery: The Treatment Principle

Stereotactic radiosurgery has been developed for the precise and complete destruction of circumscribed intracranial target lesions that have a similar radiosensitivity to normal brain tissue, without significant concomitant radiation damage to these normal adjacent structures. Interstitial radiosurgery as a local treatment is performed by direct temporary placement of single or multiple radioactive sources (“seeds”) into the target volume. Interstitial radiosurgery (formerly termed brachytherapy) has been widely accepted since 1914 for the treatment of parenchymal brain tumors.

Whereas both interstitial radiosurgery and external focused beam radiosurgery apply high doses within a stereotactically defined target volume, there are major differences regarding the spatial and temporal distribution of the radiation dose that affect risks and benefits of the therapy. In contrast to standard radiotherapy, the destructive radiographs resulting from 125I decay attenuate with a steep spatial gradient, confining the administered radia-
tion dose to the selected lesion of interest. Energy delivery close to the source is extremely high, with a steep falloff to the periphery, leading to a highly focused centrifugal zone of coagulation necrosis, surrounded by a tissue layer undergoing programmed cell death. Necrotic tissue is then removed by macrophage activity.\(^3\) Whereas a high-dose zone (200 Gy isodose) within the target volume is achieved, there is minor radiation injury outside the target. Regionally, temporary changes in capillary permeability can result in edema, and decreased local cerebral blood flow may occur. These changes can be associated with transient side effects, depending on the target volume and brain region that is treated.

In addition, the delivery of radiation from the stereotactically implanted seed occurs over a relatively protracted period of 3 weeks. This results in a much lower dose rate (1-15 cGy/h) in comparison to external-beam radiosurgery, which offers radiobiological advantages. Tumor regrowth during (or after) treatment is not a problem for patients harboring HH (as opposed to gliomas and other malignancies). The relatively protracted course of local radiation therapy therefore results in an ultimate form of fractionation that allows the surrounding normal brain structures to recover from the radiation exposure that is received. Relatively radiosensitive structures that are in close proximity to the HH, such as the optic nerves and tracts, mammillary bodies, and brainstem, thus are placed at low risk for radiation injury. The increased therapeutic ratio of radiation exposure allows interstitial radiosurgery to be performed repeatedly if the initial treatment does not result in complete seizure control.

Risk calculations for interstitial radiosurgery derived from a large population of patients with low-grade gliomas have determined that radiogenic complications occur in less than 3% of patients with treatment volumes of 23 cm\(^3\) and less.\(^4\) The vast majority of HH lesions have a volume of less than 10 cm\(^3\).

Technically, the first step involves accurate definition of the target volume, and of adjacent radiosensitive structures, using high-resolution magnetic resonance imaging (MRI). Targeting is performed by using MRI data and intraoperative computed tomography (CT) image fusion and 3-dimensional modeling. Dosimetry is performed to assure coverage of the target volume according to calculated isodoses (Fig. 1). A temporary seed (size 4.5 × 0.5 mm) containing the radiograph radiation emitter (\(^{125}\)I) in a Teflon catheter is then introduced stereotactically into the target, which is marked by a titanium ball for imaging confirmation. Correct placement is confirmed postimplantation by using MR scanning. The removal of the seed is performed after a period of about 3 to 4 weeks depending on the dose rates chosen. Both implantation and removal can in principle be performed under local anesthesia. However, in the patient group reported here, most implantations were performed under general anesthesia due to insufficient patient cooperation.

### Clinical Characteristics of an HH Patient Subgroup of Children and Adolescents Treated in Freiburg

Interstitial radiosurgery can be performed successfully in both adults and in children aged 3 years and older. We report here on a subgroup of children and adolescents (n = 15; mean age, 13.9 years at the time of radiosurgical treatment [range, 3-20 years]) who have been treated at the Freiburg epilepsy center during recent years.

All patients suffered from gelastic epilepsy caused by HH. Based on history, the mean age at epilepsy onset was 4.2 years, corresponding to a latency of 9.7 years from epilepsy onset to stereotactic treatment. All patients had been refractory to various antiepilepsy drugs (AEDs). At the time of radiosurgical treatment, 5 patients were treated with AED monotherapy and 10 with multiple AEDs. The mean number of AEDs was 1.8 (range, 1-3).

Despite AED treatment, patients suffered from seizures with gelastic component (100%), complex partial seizures (90%), tonic seizures (60%), and secondarily generalized tonic-clonic seizures (70%) before radiosurgical intervention. Complex partial seizures most often had characteristics of temporal lobe seizures with staring and oroalimentary and manual automatisms. Seizure frequencies were often exceedingly high, particularly regarding gelastic seizures, which were reported up to 300 seizures per month. Mean seizure frequency for gelastic seizures was 86 seizures per month, for complex partial seizures 51 per month, and for tonic seizures 27 per month. In contrast, secondarily generalized seizures were less frequent (mean, 3.1 per month).

Patients underwent a comprehensive presurgical evaluation including video-encephalographic recordings of seizures, structural and functional imaging, clinical neurologic examination, neuropsychological assessment adapted to the often-reduced ability of patients to cooperate, and assessment of visual fields by Goldman perimeter. Endocrinologic evaluation included assays for thyroid-stimulating hormone, T3, T4, adrenocorticotropic hormone, growth hormone, luteinizing hormone, follicle-stimulating hormone, prolactin, cortisol, dehydroepiandrosterone sulfate, and insulin-like growth factor-1 before stereotactic intervention and again 3 months after treatment.

Hemartomas were identified as cortex-isointense or slightly T2-hyperintense/T1-hypointense lesions using high-resolution MRI.\(^3\) All patients had intrahypothalamic hemartomas of Valdueza type II. The mean diameter of the HH lesions was 20.2 mm (range, 13.4-27.8 mm), and the mean volume was 1.1 cm\(^3\) (range, 0.5-3.8 cm\(^3\)). Three of 15 patients (20%) had developed central precocious puberty. One patient had polydactyly, suggesting the diagnosis of Pallister-Hall syndrome. Twelve of 15 patients (80%) had developmental retardation, whereas 3 patients had a normal IQ and performed normally in school. In 1 of these patients, however, an exacerbation of seizure activity had been associated with learning difficulties. Eleven of 15 patients (73%) suf-
ffered from behavioral disorders, most often characterized by aggressiveness.

Stereotactic seed implantation was performed as described earlier, in most cases under general anesthesia. Dosage was individually tailored according to the HH size. The mean activity of individual seeds was 3.0 mCi (range, 1.6-5.4 mCi), and the mean duration of interstitial radiotherapy was 25.1 days (range, 18-36 days). Interstitial radiotherapy treatment consisted of stereotactic placement of a single seed per implantation. Seeds were implanted twice in 8 patients (53%) and 3 times in 1 patient (7%). The repeated implantation was offered to patients in whom therapeutic efficacy of the first implantation was insufficient or if seizures relapsed within 2 years after the initial treatment. Whereas the early implantations in this case series used relatively conservative total radiation exposure to avoid possible side effects, the energy dose rates were gradually increased in view of good tolerability, ranging from 7.4 cGy/h to 17.7 cGy/h.

Comprehensive outcome assessment was performed 3, 6, 12, 24, and 36 months after initial seed implantation and classified according to Engel and Rasmussen. This included clinical neurologic examination, visual fields, electroencephalograms, MRI, endocrinologic parameters, and neuropsychological test batteries.

**Efficacy of Interstitial Radiosurgery**

At the last follow-up (after a mean period of 13.9 months after the last treatment initiation), 40% of patients had an Engel I outcome, 13% Engel II (90% reduction in seizure frequency), 20% Engel III (75% reduction in seizure frequency), and 27% were Engel IV with less improvement or no effect of treatment (Fig. 2). Of the 40% with Engel I outcome, 20% were completely free from seizures (Engel class IA), and 20% experienced residual episodes manifesting as a feeling of mirth, most likely representing simple partial seizures (gelastic auras) (Engel class IB).
Treatment effects occurred within 8 weeks after seed implantation and remained stable thereafter in most patients. In 3 patients who were initial responders, seizures reoccurred within 2 years, leading to another implantation that resulted in complete seizure control. There were, however, patients who did not profit at all from the treatment with regard to seizure frequency and severity. This included the single patient who underwent 3 consecutive $^{125}$I implantations, and another patient who had linear accelerator (LINAC) radiosurgery of the HH after unsuccessful interstitial radiosurgery, again without any beneficial effect.

Engel I outcome was associated with a complete cessation of interictal spiking in the encephalogram in 3 of 6 patients (50%) (Fig. 3) and improved neuropsychological test results in 4 of 6 patients (67%). However, improvement in the encephalogram and/or neuropsychological functioning was also observed in some patients with Engel II or III outcome. Four patients (27%) showed a reduction in the volume of the HH on repeated MRI after interstitial radiosurgery, whereas there was no clear-cut change in hamartoma size in the majority of patients.

**Tolerability of Interstitial Radiosurgery**

**Perioperative Period**

There was no perioperative morbidity, specifically, no infection or bleeding as judged by clinical assessment and postimplantation CT imaging. All patients could be discharged home on the day after seed implantation and were able to resume their everyday activities.

**Side Effects Because of Radiogenic Edema**

Follow-up MRI after $^{125}$I-seed implantation showed the development of a central necrosis at the site of implantation surrounded by a rim of increased permeability of the blood-brain barrier within the hamartoma (Fig. 4). One patient additionally developed a transient increase in the frequency of gelastic seizures 3 months after seed implantation (when other seizure types had disappeared). MRI showed edema extending to the diencephalon and surrounding white matter. The patient’s relatives had, however, also stopped antiepileptic treatment completely for fear of medication-related side effects during this period. Edema was reversible without permanent sequelae within the following months.

**Neurologic Status**

None of the patients experienced neurologic side effects or focal deficits. In particular, side effects reported using other approaches, such as oculomotor paresis or hemiparesis, were absent. All patients underwent determination of visual fields before and 3 months after implantation. Despite close proximity of several hamartomas to the optic tracts (Fig. 1), no deterioration of visual fields occurred.

**Neuropsychological Assessment**

Not all patients were able to undergo systematic testing with standard neuropsychological test batteries because of mental retardation and/or behavioral problems. Most patients with HH do have cognitive impairments because of the epileptic encephalopathy. In the patient group in whom systematic testing was possible, there were no significant negative group changes in neuropsychological performance. In the patient with transient edema, however, performance in tests of episodic memory deteriorated. No patient developed an amnesic syndrome. Overall, there was an improvement in selective attention. Results of neuropsychological testing after interstitial radiosurgery are reported in detail by Quiske and coworkers.

**Figure 2**

Outcome of interstitial radiosurgery in the subpopulation of patients <20 years of age (n = 15).
Neuropsychiatric Tolerability
As with cognition, many patients with HH have neuropsychiatric problems because of the epileptic encephalopathy. As with other treatment methods, interstitial radiosurgery resulted in considerable behavioral improvements in patients profiting from therapy.\textsuperscript{10} According to the parent’s report, 1 patient with Engel II outcome who also showed improved vigilance after treatment was reported to be more difficult to handle and to react more often aggressively. No other newly emerging psychiatric problems were noted.

Hormonal Status
Systematic assessment of hormonal parameters three and 12 months after stereotactic seed implantation did not reveal treatment-related hormonal disturbances. In particular, there were no patients with hypothyroidism or postoperative electrolyte imbalance. No patient experienced poikilothermia. Three patients, however, developed weight gain that was moderate in two (5 kg and 6 kg, respectively, at last follow-up), but severe in one patient (20 kg), despite attempts at dietary intervention.

Overall Role of Interstitial Radiosurgery in HH Treatment
The results in this group of treated children and adolescents show that we are able to completely control or significantly improve the epileptic seizures in 53\% of patients (Engel class I and II) by using interstitial radiosurgery. In several of these, not only were seizures improved or completely abolished, but improvements were also noted in behavior and neuropsychological performance in the domains of attention and ability to concentrate. It has to be noted, however, that about 40\% of patients remained in whom the effect on seizure frequency was less impressive or even absent. Regarding the high baseline seizure frequency before intervention, even a

Figure 3 Representative electroencephalographic segments of a 16-year-old HH patient with refractory epilepsy. (A) Electroencephalographic sample preceding \textsuperscript{125}I seed implantation and (B) 3 months after treatment. This patient was completely free of seizures after interstitial radiosurgery.
proving its role in therapeutic failures.15 No posttreatment intracranial recordings available that could support a possible role of secondary epileptogenesis in the development of different seizure types. However, there are invasive recordings of several groups, including our own, eradicating by the treatment. In 1 patient who failed repeated treatments with interstitial radiosurgery, a transcallosal resection of possible remnants of the HH was performed, leading to only transient improvement in seizure control.

The outcome results reported here are similar to those obtained with gamma knife radiosurgery, as reported in the largest series by Regis and coworkers.11 However, the report by Mathieu and coworkers12 and our own experience with a smaller series of patients treated by LINAC radiosurgery had less favorable results. In particular, Engel class I outcome was not achieved.

The results of surgical resection suggest that the number of patients becoming completely seizure free can be higher than 50%.13,14 So far, however, 40% to 60% of patients do not achieve complete seizure control with any treatment offered.11 This raises the issue of a possible role of secondary epileptogenesis in areas synaptically connected to the HH. Invasive recordings of several groups, including our own, support a possible role of secondary epileptogenesis in the development of different seizure types. However, there are no posttreatment intracranial recordings available that could prove its role in therapeutic failures.15

Figure 4 Typical radiologic sequelae after interstitial radiosurgery (T1-weighted sagittal section with gadolinium contrast enhancement). The treated HH lesion shows a central cavity of radionecrosis with a surrounding rim of increased capillary permeability.

Time Course of Therapeutic Effect

When comparing different treatment options in patients with gelastic epilepsy associated with HH, not only efficacy in seizure control but also the time course of onset of efficacy and the risk for side effects have to be considered. Interstitial radiosurgery showed its effects within weeks after initiation of treatment. Thus, all patients showing an effect on seizure frequency reached the peak efficacy within 2 to 8 weeks. With 1 exception noted previously, there was no period of increased seizure frequency or severity.

Interestingly, as compared with surgical approaches directly removing or disconnecting the epileptogenic tissue, the time course is similar. Microsurgical resection of HH may not result in immediate seizure cessation but may show its efficacy only after weeks to several months (the “running down” phenomenon). This observation also suggests the contribution of secondary (presumably neocortical) foci to seizure generation.13,14,16 A period of weeks to a few months, however, is acceptable to most patients and allows reasonably quick decisions on the necessity of future therapeutic steps.

Comparing the time course of efficacy to other radiosurgical approaches like LINAC or gamma knife surgery, the onset of action with interstitial radiosurgery offers considerable advantages. As recently reported in detail, gamma knife radiosurgery, although similarly effective as interstitial radiosurgery, needs a much longer time course to result in seizure abatement or control.11 In addition, there are phases during which seizure frequency and/or intensity may increase. Regis and coworkers11 thus state that a minimum of 3 years of follow-up after gamma knife radiosurgery is mandatory before final evaluation of efficacy and possible decisions with regard to a repeated treatment.11 The authors report 5 post-treatment epochs, extending up to more than 50 months, including a subgroup of patients with a period of seizure clustering for days to weeks before seizure frequency diminishes. When taking the severity of the uncontrolled disease into consideration, this long time course may be a relevant disadvantage of this otherwise well-tolerated radiosurgical approach.

Treatment-Related Side Effects: An Overview

A major incentive to develop new treatment strategies for HH was not only the insufficient efficacy of early microsurgical approaches but also the high risk associated with surgical resection. This is because not only of possible hormonal complications resulting from removal of hypothalamic tissue but also the close spatial relationship of the HH to adjacent vital structures, such as the mammillary bodies and optic tracts. In addition, structures encountered on the way during the surgical approach to the hypothalamus are at risk, depending on the specific approach. For example, the columns of the fornices are at risk with the transcallosal approach, and major
vessels are encountered with a lateral pterional approach. When assessing the role of interstitial radiosurgery, a comparison of side effects with those occurring with microsurgical resection is thus of importance.

Perioperative meningitis has been reported after endoscopic resection via the third ventricle. One patient was reported to have died on the day after attempted surgical removal of an HH. Neurologic deficits resulting from surgical resection of HH have been reported in relation to several available approaches: oculomotor palsy after microsurgery, stereotactic thermocoagulation, hemiparesis or hemiplegia by thalamocapsular infarcts after microsurgery and endoscopic resection via the third ventricle, brainstem infarction after stereotactic thermocoagulation, and visual field defects after microsurgical resection with pterional and transcallosal-interforrniceal approach.

The neuropsychological consequences of treatment include transient and persistent memory deficits after transcallosal approaches. This has to be weighed against possible cognitive improvements in patients with good seizure outcome as reported in several series.

A variety of endocrine disturbances may occur with intrahypothalamic interventions because of the crucial role of the hypothalamus in endocrine control. Central diabetes insipidus has occurred after microsurgical resection, following endoscopic resection via the third ventricle, and after transcallosal-interforrniceal resection. Panhypopituitarism has been observed after endoscopic resection via the third ventricle, and hypothyroidism and growth hormone deficiency have been reported after transcallosal and endoscopic resection via the third ventricle. Transient hypernatremia was reported after transcallosal-interforrniceal HH resection in more than 50% of patients. Finally, hyperphagia occurred in up to a third of patients after a transcallosal-interforrniceal resective approach as a consequence of microsurgical resection with conventional approaches, after endoscopic resection via the third ventricle, and after intrahypothalamic stimulation.

Neuropsychiatric complications manifesting as psychosis have been reported to occur in 2 patients with a history of prior psychiatric disturbances after transcallosal resection of hamartomas.

Of these treatment-related side effects, only persistent hyperphagia leading to obesity was observed so far using interstitial radiosurgery in 1 patient of this series and in another patient treated in adulthood who is not reported here. In addition, edema after interstitial radiosurgery may result in headache, fatigue, and transient increase of seizure frequency.

Applicability of Interstitial Radiosurgery

Regarding applicability of interstitial radiosurgery, there are limits related to the size of the HH lesion. The largest size that can be treated with interstitial radiosurgery is 3 cm in diameter. Giant hamartomas (sometimes classified as type VI in the HH classification proposed by Regis and coworkers and type IV in the classification proposed by Delalande and Fohlen) are not candidates for treatment based on interstitial radiosurgery alone. This restriction by size similarly applies to other radiosurgical approaches, and larger hamartomas are certainly better treated with microsurgical resection. On the other hand, 1 recent series has shown that the likelihood of complete resection (using the transcallosal approach) appears to decrease with increasing HH volume and that success for seizure control relates to the percentage of the lesion that is resected. Possibly, a combination of initial surgical resection and subsequent radiosurgery may be an option for these patients.

In the majority of patients with HH, however, not the size but the location and the immediate neighborhood relationships between the HH and radiosensitive structures like the optic nerves and tracts and the mammillary bodies are critical for the applicability of radiosurgical treatments. In our hands, several patients who had been considered possible candidates for LINAC radiosurgery were refused this treatment because of a high risk of damaging the optic tracts with radiation intensities above 10 Gy. Interstitial radiosurgery was performed in these patients without any side effects, as reported previously. This points to an advantage of interstitial radiosurgery as compared with other radiosurgical approaches, related to decreased exposure of surrounding normal tissue because of the rapid spatial decay of radiation arising from seeds. Additionally, the protracted release of radiation over a period of several weeks allows adjacent structures to tolerate higher total radiation dosages applied to the target structure.

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