Interstitial radiosurgery in the treatment of gelastic epilepsy due to hypothalamic hamartomas

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Abstract—The authors evaluated a new stereotactic radiosurgical approach in seven patients with gelastic epilepsy due to hypothalamic hamartomas. Stereotactic implantation of ^{125}I-seeds into the hamartoma was feasible in six patients. At follow-up at least 1 year after interstitial radiotherapy, two patients had become seizure-free within 2 months, and two others had only persisting auras. There were no major perioperative or postoperative side effects.

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Hypothalamic hamartomas often cause pharmacoresistent epilepsy with gelastic seizures and other seizure types,[1,2] leading to developmental impairment and often constituting a catastrophic epilepsy of childhood.[3] Microsurgical resection of hypothalamic hamartomas carries a high risk (e.g., of diabetes insipidus, hyperphagia, hypopituitarism, Korsakoff's syndrome, thalamic infarctions, and central pareses), and seizure control may be poor if resections remain incomplete, which is a particular problem in intrahypothalamic and sessile hamartomas (types IIa and IIb[4]).

There is thus a need for alternative therapeutic strategies. Recently, aside from improved neurosurgical techniques such as transcallosal resection, external radiosurgery using gamma-knife or LINAC[5] have been used with promising results. We report on the method and outcome of treatment of gelastic epilepsy due to hypothalamic hamartomas by interstitial radiosurgery using temporary ^{125}I-seeds[6,7] stereotactically implanted into hamartomas in seven patients with follow-up periods of 12 to 36 months.

Patients and methods. Seven consecutive patients (six male, one female, aged 9 to 31 years, mean age 17 years) with pharmacorefractory gelastic epilepsy were included in this analysis. All patients had gelastic seizures, complex partial seizures with often tonic components, and secondarily generalized tonic clonic seizures. Apart from an initial funny feeling evolving into gelastic seizures, one patient had auras with epigastric discomfort, and one patient had simple partial seizures with a tingling epigastric sensation evolving into manual and oral automatisms and behavioral dyscontrol with preserved responsiveness. The mean duration of epilepsy before the first radiosurgical intervention was 14.3 years (range 7 to 28 years); the mean seizure frequency under medical therapy ranged from 10 to more than 500 seizures per month. Two patients had precocious puberty; one patient had bilateral polydactylia suggesting Pallister-Hall syndrome. All patients and the parents of children younger than 18 years gave their informed consent to the use of interstitial radiosurgery in the treatment of their epilepsy. Patient characteristics are summarized in the table.

Diagnostic procedures. Gelastic epilepsy was documented by video-EEG telemetry using surface electrodes and additional depth electrode recordings in 5/7 patients. An underlying hypothalamic hamartoma was demonstrated by high resolution MR imaging. Before radiosurgery, and 3 and 12 months afterwards, visual fields, basal hormone levels, and comprehensive neuropsychological testing were obtained.

Stereotactic procedure. Depending on the individual patient's ability to cooperate, stereotactic procedures were performed under local anesthesia in 3/7 and under general anesthesia in 4/7 patients via a right frontal approach. When stereotactic biopsies had been obtained, ^{125}I-seeds with a diameter of 0.5 mm were implanted with dosages derived from computer modeling of target volume; the reference dosage was chosen as 60 Gy at the outer margin of the hamartoma. The mean activity of individual seeds as measured in an isotope calibrator counter (PTW, Freiburg, Germany) was 2.35 ± 0.6 mCi, and the mean energy dose rate was 10.5 ± 3.1 cGy/hour. Calculated isodoses superimposed on the surrounding structures are shown in figure 1. The correct position of the seed was ascertained on T1–3D MR data sets on the day after implantation. Seeds were removed from the hamartomas under local anesthesia after a mean period of 24.0 ± 5.7 days.

Outcome. Outcome classification was performed according to the recent proposal of the International League Against Epilepsy.[8] Medical treatment was kept constant at least for 12 months after radiosurgery, if possible.

Results. MR imaging showed unilateral mesial intrahypothalamic lesions with a diameter of 8 to 11 mm (mean 10.0 ± 1.1 mm; see the table), which in part bulged into the third ventricle (figure 2, A and B). Stereotactic placement of the ^{125}I-seed was performed successfully in 5/7 patients as confirmed by MR imaging (see figure 2). In Patient 5, the seed was not placed in the exact center of the hamartoma, and in Patient 7, two attempts to insert the seed into the hamartoma failed due to the coarse consistency of the hamartoma, and seeds were removed immediately.

Outcome in terms of seizure reduction was class I (com-

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Table *Patient data*

Patient/Sex	Seizure types	Seizure frequency per mo	Pharmaco resistance	Hamartoma diameter, min/ age at onset of epilepsy, y	Age at implantation, y	Follow-up period, mo	Medication at time of presurgical evaluation, mg/d	Present medication, mg/d	Outcome
1/M	E, G, CPS, GM	 30 10–15 <1	CBZ, DPH, LTG, PRI, VPA	11/3	31	26	CBZ 800 LTG 450	LTG 400	I
2/M	G, CPS, GM	10 1 0 (with AED)	CBZ, LIT, VPA, VGB	11/10	16 17	24	CBZ 1,700 LTG 350	LTG 1,150	I
3/M	G, CPS, GM	>500 120	CBZ, LTG, VPA, VGB	10/2	9 10 11	24	CBZ 1,000 LTG 350	CBZ 800 LTG 350	II
4/M	G, CPS, GM	 60 Rare	CBZ, DPH, STH, VPA	9/<1	10	18	CLB 20 LEV 2,000 TPM 100	LEV 2,000 TPM 100	IV
5/M	G, CPS, GM	60 120 7	Br, CBZ, CZB, LEV, LTG, PRI, VPA	8/<1	14 15	15	LEV 3,000 LTG 300	LEV 3,000 LTG 300	III
6/M	E, G, CPS, GM	 8 5–10 Rare	VPA, OXC	11/2	18	12	VPA 2,400 OXC 900	OXC 1,800	II
7/F	G, CPS, GM	5 10	CBZ, CZB, ESM, GBP, LTG, PB, PRI, VGB, VPA and VNS	10/<1	22 23	36	CBZ 1,200 CLB 10 GBP 2,400	DPH 300 LEV 4,000 OXC 1,800	V (presently >90% seizure reduction 18 months after LINAC radiosurgery)

All hamartomas were type IIb, according to reference 4; outcome classification was performed according to reference 8. E = epigastric aura; G = gelastic seizure; CPS = complex partial seizures; GM = secondarily generalized seizure; CBZ = carbamazepine; DPH = phenytoin; LTG = lamotrigine; PRI = primidone; VPA = valproic acid; AED = antiepileptic drugs; VGB = vigabatrin; STH = sulthiame; CLB = clobazam; LEV = levetiracetam; TPM = topiramate; Br = brome; OXC = oxcarbazepine; ESM = ethosuximide; GBP = gabapentin; PB = phenobarbital; VNS = vagus nerve stimulation; LINAC = linear accelerator.

plete seizure freedom) in two patients, class II (recurrence of auras with a tingling sensation in the head or persisting epigastric discomfort) in two patients, and class III through V in one patient each. In Patient 5, the formerly predominant gelastic seizures were completely controlled and secondarily generalized tonic-clonic seizures were reduced, but he yet had disabling brief complex partial seizures with falls. Patient 4 continued to have complex partial seizures at a lower frequency but overall did not profit from the intervention (see the table). Seizure outcome was not related to a reduction in the size of the remaining hamartoma.

In the patients rendered seizure-free, two complex partial seizures occurred within the first 2 months after seed implantation in Patient 1 and one complex partial seizure 4 weeks after seed implantation in Patient 2 before definite cessation of seizures. Anticonvulsive medication of the two seizure-free patients has so far been reduced to a monotherapy.

Additional investigations. There were no consistent postoperative changes in the neuropsychological performance, no impairments of visual fields, and no postoperative changes in baseline blood levels of thyroid stimulating hormone, T3, T4, adrenocorticotrophic hormone, growth hormone, luteinizing hormone, follicle stimulating hormone, prolactin, cortisol, dehydroepiandrosterone sulfate, or insulin like growth factor-1. There was no perioperative morbidity.

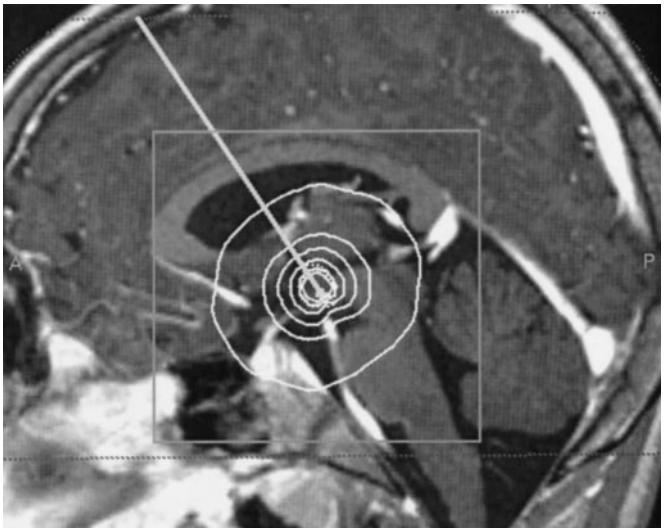

Figure 1. Trajectory for stereotactic biopsy, implantation of recording electrodes, and ^{125}I-seed (yellow). In this particular patient, activity of the seed was 2.0 mCi, and the seed remained for a period of 25 days within the hamartoma. Calculated isodoses applied during this period are indicated by circles of increasing diameter: 60 Gy (innermost), 40 Gy, 20 Gy, 10 Gy, 5 Gy, and 1 Gy (outermost).

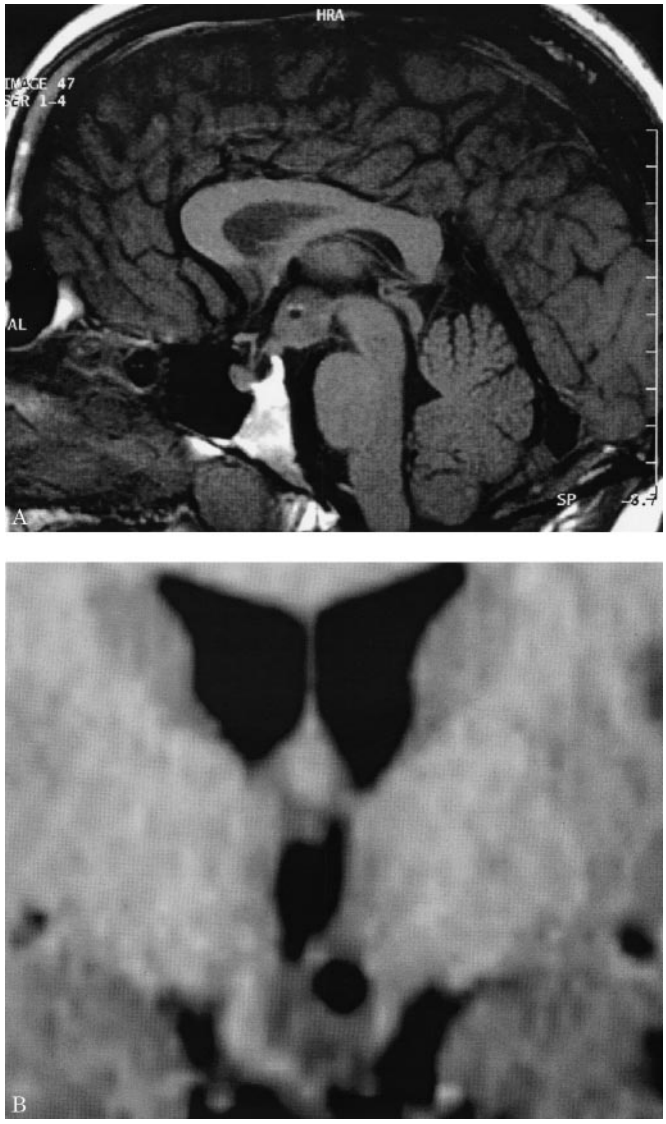

Figure 2. Intrahypothalamic hamartoma as seen on sagittal and coronal T1-weighted MR slices. A, B) Midsagittal and coronal T1-weighted MRI sections 3 months after intrahypothalamic implantation of a ^{125}I seed (the biopsy site is indicated by a hypointense titanium ball, diameter: 0.5 mm). (Courtesy of Prof. Schumacher, Dept. Neuroradiology, University Clinic of Freiburg.)

Discussion. The present series shows that stereotactic interstitial radiosurgery is an effective and safe treatment of gelastic epilepsy due to hypothalamic hamartomas. Seizure freedom was achieved in 2/6 patients in whom a seed placement within the hamartoma was possible. In two more patients, only auras 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 after seed implantation; this compares favorably with gamma knife radiosurgery, in which a median latency in seizure cessation of 9 months was reported.[5]

Three patients had to be reimplanted as the first intervention did not lead to complete and persisting seizure control. It is of interest that incomplete destruction of the hypothalamic hamartoma can lead to the disappearance of only some seizure types formerly present. The diversity of seizure types has been one reason to claim widespread cortical changes underlying the epileptic syndrome.[9] The failure to control all seizure types by surgery of the hamartoma may, however, not be related to such a multifocal origin of the epilepsy, as repeated intrahypothalamic interstitial radiosurgery resulted in control of the other seizure types, too, in two of our patients. This rather points to different networks involved in the spread of ictal epileptic activity in different seizure types.

In this pilot series, no side effects of stereotactic seed implantation were noted despite close monitoring of patients within the first year after radiosurgery. This is a clear advantage over open microsurgery, which carries a serious risk of permanent neurologic and endocrine sequelae. It is of particular importance that radiosensitive structures like the optical tract, mamillary bodies, and brainstem that are in close vicinity to the location of the hamartoma appear unimpaired. The principle of interstitial radiosurgery may be advantageous in avoiding potential radiation-induced side effects as the application of gamma radiation from the center of the lesion can be performed with minimal exposition of extralesional brain tissue to gamma radiation (see figure 1). The energy of gamma radiation emitted by ^{125}I is in the range of 27 to 35 keV and thus far lower than that used with external radiation; it is thus effectively attenuated by interposed tissue, which spares normal tissue during brachytherapy.[10] In addition, the protracted delivery of radiation from the im-

planted seed at a low dose rate (1 to 100 cGy/h) as compared to >1 Gy/min with external-beam radiosurgery allows the application of high local total doses to the target volume with a minimal risk of radiation damage to surrounding healthy brain structures.[6] This increases the therapeutic ratio and allows for repeated seed implantations if the initial effect is incomplete. In principle, the maximal diameter of a structure that can be treated using a single ^{125}I-seed is 3 cm, which would allow treatment of the vast majority of intrahypothalamic hamartomas.

Possible advantages of interstitial radiosurgery may be the minimal exposure of extralesional brain tissue to gamma radiation, the opportunity to combine its use with stereotactic tissue biopsy and depth recordings, and a rapid onset of seizure control as suggested by the outcome results. There are patients in whom a central stereotactic seed placement is impossible due to the coarse consistency of the hamartoma. These patients may be better controlled by LINAC or gamma-knife radiosurgery. Larger series with longer follow-up periods will be necessary to compare stereotactic interstitial radiosurgery, external radiation, and transcallosal resection with regard to their long-term efficacy and possible side effects.

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