

# Intractable epilepsy following radiosurgery for arteriovenous malformation

## Case report

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✓ Radiosurgery is often used to treat arteriovenous malformations (AVMs) located in deep brain locations. Most of these procedures are successful not only in obliterating the AVM but also in decreasing the frequency and severity of associated seizures. Although radiosurgery is occasionally associated with the development of easy-to-control seizures immediately postoperatively, there have been no reports of intractable epilepsy developing after radiosurgery. In this report, however, a case is presented in which a patient underwent gamma knife surgery (GKS) for an AVM, after which intractable epilepsy and mesial temporal sclerosis (MTS) gradually developed.

A 37-year-old right-handed woman underwent GKS for a right mesial parietotemporooccipital AVM. One year later, the AVM had reduced in size, but the patient began to experience complex partial seizures (CPSs). These CPSs initially occurred at a frequency of one per month, but 6 months later they were occurring every other week. She also started having secondarily generalized tonic-clonic seizures (GTCSs) once per month. Over the next year the frequency of her seizures gradually increased to several CPSs per day and two to three GTCSs per week, despite treatment with various combinations of antiepileptic drugs. By this time her AVM had decreased to one half of its original size. Video-electroencephalography monitoring demonstrated that both the CPSs and GTCSs were arising from the right posterior quadrant. Magnetic resonance imaging revealed not only the presence of the right-sided AVM, but also right-sided MTS. The patient underwent surgical resection of the AVM and right temporal lobectomy. She has been free from seizure for longer than 1 year.

Radiosurgery may be associated with intractable epilepsy and MTS.

**KEY WORDS** • epilepsy • mesial temporal sclerosis • arteriovenous malformation • gamma knife surgery

**R**ADIOSURGERY was pioneered by Leksell<sup>7</sup> and is defined as the closed-skull destruction of an intracranial target in a single session by using ionizing beams of radiation that are focused with the aid of an intracranial guiding device.<sup>7</sup> Leksell used gamma nuclides, and cobalt-60 became the most widely used nuclide.<sup>15</sup> This procedure is known as GKS.

*Abbreviations used in this paper:* AVM = arteriovenous malformation; CPS = complex partial seizure; EEG = electroencephalography; GKS = gamma knife surgery; MR = magnetic resonance; MTS = mesial temporal sclerosis.

In the early years after its inception, GKS was used primarily to treat functional neurological cases such as pain and tremor. Over the years, GKS has been found to have applications in a number of treatment settings, including cerebral AVMs, other types of vascular malformations, benign and malignant brain tumors, metastatic brain tumors, and amygdalohippocampectomies for intractable epilepsy.

Patients with AVMs usually present after having sustained an intracerebral hemorrhage; in a minority of cases, seizures and headaches may be the presenting complaint.<sup>8</sup>

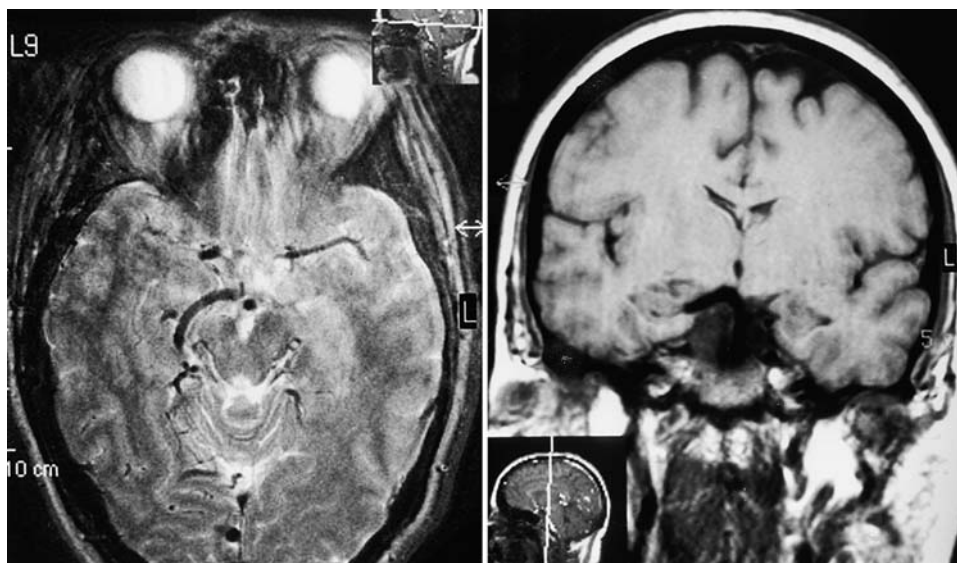


FIG. 1. *Left:* Axial T<sub>2</sub>-weighted MR image obtained before radiosurgery, demonstrating the spatial relation of the AVM to the right mesial temporal lobe. *Right:* Coronal T<sub>1</sub>-weighted MR image obtained before radiosurgery, demonstrating hippocampal anatomy. Notice the close relation of the AVM to the right mesial temporal structures.

In some patients, the AVMs are located in critical brain regions and cannot be safely resected. These cases are especially suited for GKS. Gamma knife surgery results in proliferation of endothelial cells leading to luminal closure and obliteration of the AVM;<sup>11</sup> this process generally takes between 1 and 3 years following the procedure. When the AVM is associated with seizures, seizure control generally improves after radiosurgery.<sup>3,13,14</sup> We report the case of a patient in whom intractable epilepsy with MTS developed following GKS. To the best of our knowledge, such a complication has not been described previously.

### Case Presentation

*History.* This 37-year-old, right-handed woman began to experience numbness in her left arm 3 years ago. She attributed this to local trauma, but within 2 weeks the numbness had spread to involve the whole left side of her body. Difficulty in left hand coordination and left-sided gait were also noted at that time.

*Examination and Radiosurgery.* An MR image revealed an AVM around the right lateral ventricle invading the occipital horn (Figs. 1 and 2). Because the AVM was thought to be in a location that is not easily accessible microsurgically, the patient was referred for GKS.

In June 1997, the patient underwent GKS with anesthesia monitoring in the operating room. Prior to the radiosurgery, stereotactic angiography and MR imaging were performed, revealing the previously identified AVM in the right medial temporoparietooccipital region. The AVM measured 37 × 27 × 18 mm (volume 18 cm<sup>3</sup>) and was supplied primarily by branches of the right posterior cerebral artery. The entire AVM was included in the radiosurgical field and five isocenters were chosen. The isodose configuration was chosen with the assistance of a com-

puter system (Leksell GammaPlan; Elekta Instruments AB, Stockholm, Sweden). The AVM was included in the 50% isodose configuration. The tissue volumes included in the isodose configuration were as follows: 10%, 65.25 cm<sup>3</sup>; 20%, 27.2 cm<sup>3</sup>; 30%, 14.43 cm<sup>3</sup>; 40%, 9.38 cm<sup>3</sup>; 50%, 6.7 cm<sup>3</sup>; 60%, 3.56 cm<sup>3</sup>; 70%, 1.23 cm<sup>3</sup>; 80%, 0.32 cm<sup>3</sup>; and 90%, 0.08 cm<sup>3</sup>. Treatment durations were 6.29, 6.25, 6.24, 6.6, and 6.28 minutes. Thirty-six grays were delivered as a maximum dose, with the periphery of the lesion receiving 18 Gy. No immediate complications were noted and the patient was discharged from the hospital on the following day.

*First Postoperative Course.* The patient did well until July 1998 when she experienced a prolonged tonic-clonic seizure. She was admitted to a local hospital and was treated with phenytoin. Despite therapeutic levels of phenytoin, she continued to have CPSs. These seizures were stereotypical and started with an aura of feeling nervous followed by loud swallowing sounds. She would then close her eyes and not respond to verbal commands. Within a few seconds she would exhibit lip pouting, lip smacking, chewing movements, and manual automatisms of both hands. This activity would continue for several minutes and then cease, at which time the patient described feeling nauseated and began to hiccup. At this point she would be able to follow simple commands, but was not oriented. Over the next several minutes her condition would gradually return to baseline. The seizures lasted 4 to 5 minutes and occurred at a frequency of one per month.

*Second Examination and Medical Treatment.* The patient was seen at our center in December 1998 for consideration of AVM resection. A repeated MR image and cerebral angiogram revealed a one-third reduction in the size of the AVM and microsurgical excision was postponed. Post-radiosurgical cysts or hemorrhages were not noted. The

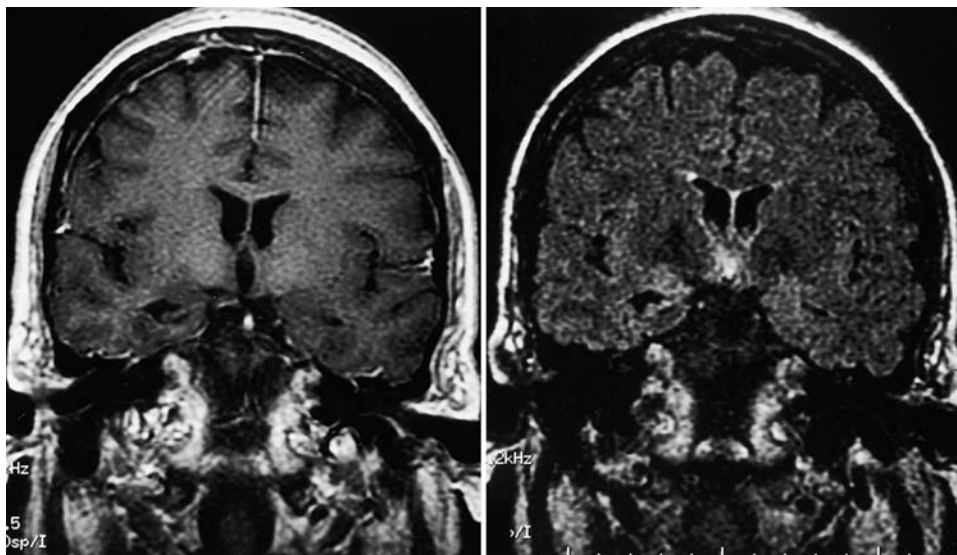


FIG. 2. *Left:* Coronal T<sub>1</sub>-weighted MR image obtained postradiosurgery, demonstrating right hippocampal atrophy. *Right:* Coronal fluid-attenuated inversion-recovery MR image demonstrating an increased signal in the right hippocampus.

frequency of her seizures had increased to one CPS every week, and she had tried carbamazepine in addition to phenytoin in monotherapy. Over the next 9 months the frequency of the patient's seizures gradually increased despite aggressive management with numerous antiepileptic drugs in monotherapy and combination therapy. In August 1999 she was admitted for video-EEG monitoring. At that time she was experiencing CPSs daily and generalized tonic-clonic seizures twice a week. Medication regimens that had been tried included phenytoin, carbamazepine, valproic acid, gabapentin, lamotrigine, tiagabine and topiramate in high doses and various combinations. Four seizures were captured; all were stereotypical with signs being similar to those described earlier. Electrographically, the seizures were characterized by recurrent spike-and-wave discharges that were phase reversing at the F4 electrode, followed by rhythmic 4- to 6-Hz theta activity located predominantly over the right temporal area. The electrographic seizure activity continued for approximately 7 minutes and was followed by diffuse slowing, most remarkable in the right temporal region. A repeated cerebral angiogram and an MR image revealed the AVM to be approximately one half of its original size; right-sided MTS was also noted on the MR image (Fig. 2).

After further medical intervention using antiepileptic drugs, the patient's epilepsy continued to be intractable and increased in severity. In February 2000 a repeated MR image and cerebral angiogram revealed no changes from the studies obtained in August 1999.

*Second Operation and Postoperative Course.* The patient subsequently underwent microsurgical excision of the AVM and a right-sided anterior temporal lobectomy. Unfortunately, specimens of hippocampus were not submitted for histopathological evaluation. The patient has remained free from seizures since surgery and follow-up review has lasted longer than 1 year.

## Discussion

Several studies have been conducted to evaluate the effects of radiosurgery on epilepsy associated with AVMs. Sutcliffe, et al.,<sup>14</sup> reported that 60% of their 160 patients treated for AVMs associated with seizures experienced improvement in seizure control. These authors postulated that epilepsy improved in most patients because the epileptogenic area was close to the AVM and had undergone radiation treatment, thus eliminating the seizure focus. Only three patients (6%) experienced a deterioration of seizures; from the data presented, all these cases were easy to control. Falkson and colleagues<sup>3</sup> reported that 94% of their 16 patients experienced improvement in seizure control and none had worsening symptoms. Steiner and associates<sup>13</sup> noted that epilepsy improved in 70% of 59 patients; however, in 11 of their patients new-onset seizures developed after GKS. These authors ascribed these seizures to intracerebral hemorrhages that the patients had suffered prior to radiosurgery and did not elaborate on seizure control in this group of patients. Using a linear accelerator radiosurgical system, Eisenschenk, et al.,<sup>2</sup> found that in 78% of 33 patients, a considerable improvement in seizure frequency and severity was achieved. None of their patients experienced new-onset seizures postradiosurgery. In that series, patients with AVMs involving the temporal lobe exclusively or contiguous to the temporal lobe were least likely to become seizure free. In a pediatric series reported by Gerszten and associates,<sup>5</sup> 85% of 13 children with seizures associated with AVMs became seizure free after radiosurgery. In two (3%) of 72 patients seizures developed after radiosurgery; in one patient seizures were poorly controlled using a single anticonvulsant medication.

Flickinger, et al.,<sup>4</sup> recently published a multicenter report on complications following radiosurgery for AVMs. Of 1255 patients who had undergone radiosurgery,

## Intractable epilepsy after AVM radiosurgery

102 experienced complications. Twelve of these patients experienced worsening<sup>7</sup> or new-onset<sup>5</sup> seizures after radiosurgery. Seizure onset for the latter group varied between 4 months and 64 months postradiosurgery. In all these cases, seizures were well controlled with antiepileptic drugs. This led the authors to conclude that “. . . seizure(s) appear to present a less serious form of radiation injury. . . .”<sup>4</sup>

In most patients suffering from seizures associated with radiosurgery, seizure control has been easily accomplished or has not been discussed.<sup>4,5,13</sup> The case presented in this report is unique in that intractable epilepsy and MTS developed after GKS. The patient presented with seizures 13 months after she had undergone radiosurgery. The frequency of her seizures increased over the next 18 months to a point at which she was experiencing daily CPSs and weekly tonic-clonic seizures. Semiologically and electrographically, her syndrome was temporal lobe epilepsy. The delayed onset and gradual worsening of her seizures coincided with the angiographically determined reduction of her AVM. The expected time course of histological obliteration of her AVM would also be the same.<sup>11</sup>

The cause of this patient's seizures remains uncertain. The possibilities include de novo development of intractable epilepsy or a delayed effect of GKS. Although de novo development of intractable temporal lobe epilepsy is possible, it would be very unusual for it to arise during the fourth decade of life. It is possible that delayed effects of GKS could result in such a syndrome. Delayed injury and destruction to areas near the radiosurgical target site have been demonstrated. Sheline, et al.,<sup>12</sup> showed that such delayed reactions are hazards of therapeutic administration of radiation. They demonstrated that, near the sites treated with radiation, there were areas of gliosis or frank necrosis resulting from either vascular changes or demyelination. If such an injury occurs in a highly epileptogenic area such as the hippocampus, an intractable epilepsy syndrome could develop. In this case, the AVM was located in the mesial temporoparietooccipital region and, thus, the hippocampus was nearby (Fig. 1).

There are several possible causes for the changes visible on radiographs of the mesial temporal structures: recurrent seizures; hemorrhage into the hippocampus; pre-existing atrophy of the hippocampus, unveiled over time by the shrinkage of the AVM; and delayed radiation effects. The radiation effects could be a direct radiation-induced injury, demyelination, or infarction of the hippocampus due to occlusion of its blood supply. Kihlstrom and colleagues<sup>6</sup> found that in three (17%) of 18 patients undergoing GKS for AVMs, an area of hyperintensity was seen on T<sub>2</sub>-weighted MR images near the target site. These authors postulated that these areas were most likely gliosis or regions of demyelination. Regis and associates,<sup>9</sup> have also reported changes observed on MR images several months after GKS in patients who had undergone radiation treatment of the amygdalohippocampus.<sup>9</sup> Months after radiosurgery, these authors noted contrast enhancement in the 50% isodose region and a swollen hippocampus with T<sub>2</sub>-weighted signal hyperintensity.<sup>10</sup> The cases described by these authors were different from ours in that mesial temporal structures were targeted and changes in these structures were expected. In our case, the MTS was

most likely induced either by recurrent seizures or by a radiation effect, because there was no evidence of blood products within the hippocampus and close inspection of pre-GKS MR images revealed no evidence of increased T<sub>2</sub> signal in the hippocampal area.

The patient presented in this report underwent resection of the AVM in an effort to control her epilepsy. Because there was an abnormal signal within the ipsilateral hippocampus on MR images, it was elected to remove not only the AVM, but also the mesial temporal structures without further invasive EEG monitoring. This approach has been supported by Cascino, et al.,<sup>1</sup> who noted that seizure-free rates were much lower in patients with dual disease (presence of a lesion and MTS) when only a lesionectomy is performed. Thus, at our institution, a lesionectomy and resection of mesial temporal structures are performed simultaneously without further invasive EEG monitoring.

Since she underwent a right temporal lobectomy with microsurgical resection of the remaining AVM, this patient has been seizure free for longer than 1 year. We suggest that intractable epilepsy can occur as a consequence of radiosurgery of AVMs that are located in certain critical areas. One such area is adjacent to the hippocampus.

### Conclusions

Gamma knife surgery is commonly performed to treat AVMs that are surgically inaccessible or located in eloquent areas of the brain. Intractable seizures have not been reported as a significant complication in these patients. We report the case of a patient in whom intractable epilepsy and right MTS developed after GKS was performed to treat an AVM in her right temporoparietooccipital region. She has been free from seizures for longer than 1 year after she underwent a right anterior temporal lobectomy and microsurgical excision of the AVM. We suggest that radiation produced by the gamma knife may be associated with intractable epilepsy and MTS.

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