Unilateral Holmes tremor and focal dystonia after Gamma Knife surgery

Case report

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 \checkmark Holmes tremor is a rare, involuntary slow shaking in the proximal portions of the limbs during rest and voluntary motion. It occurs frequently after midbrain damage. The authors report on a 20-year-old man who developed Holmes tremor after undergoing Gamma Knife surgery for an arteriovenous malformation in the left thalamus extending to the tegmentum. This is possibly the first report of such an adverse effect after radiosurgery. The tremor was believed to be secondary to radiation-induced infarction of the midbrain.

KEY WORDS • Holmes tremor • arteriovenous malformation • Gamma Knife surgery • adverse radiation effect • radiosurgery

RTERIOVENOUS malformations of the brain are relatively uncommon, although they are a major cause ▲ of hemorrhagic stroke in the young population (<20 years of age). The risk of hemorrhage increases with patient age, volume of the AVM nidus, and in centrally located AVMs.^{5,14} Surgical removal of midbrain AVMs is especially difficult, producing high mortality and morbidity rates.¹¹ Gamma Knife surgery is now widely accepted as an important therapeutic modality.^{5,6,10,12,14} The common AREs of GKS include acute brain edema. necrosis to the brain parenchyma, cranial nerve injury, latent hemorrhagic risk, cyst formation, and new or worsened seizures.^{5,6,10,12} To the best of our knowledge, post-GKS Holmes tremor has never been reported in the English literature. The authors describe a patient with Holmes tremor that developed 2 weeks following GKS. The possible pathogenesis will be discussed and the discussion supported by neuroimaging findings.

Case Report

History and Examination. This 20-year-old right-handed man without a notable medical history suddenly became comatose. An initial CT scan of his brain revealed an in-

traventricular hemorrhage with unusual calcified spots in the left midbrain (Fig. 1A). Cerebral angiography demonstrated a large 7.4-ml AVM in the left thalamus extending to the tegmentum; the AVM was a Spetzler–Martin Grade V.¹⁵ The patient recovered from his comatose state with mild (Grade 4/5) right hemiparesis.

Operation. One year later, he underwent GKS with a margin dose of 18 Gy to the 50% isodose line; no helmet plugs were used (Fig. 1B and C).

Postoperative Course. Two weeks postoperatively the patient complained of occasional mild tremor in his right hand. The tremor became progressively worse, reaching a frequency of 3 Hz/second at rest and on intention. Focal dystonia in the right upper limb appeared approximately 3 months later. High-dose Artane (5 mg three times daily) and amantadine (100 mg twice daily) were prescribed, and regular rehabilitative therapy was initiated. An acceptable recovery status was achieved 1 year later, and 2 y, the patient had only mild intention tremor and the dystonia had abated.

The patient underwent MR imaging at regular 3-month follow-up evaluations. A small, hyperintense lesion, rather than the thrombosed infarction, was persistently visible caudomediodorsa to the left red nucleus on both DW imaging and FLAIR sequences (Fig. 2). This ischemic lesion became more prominent and progressively larger 9 months later, but seemed to have faded away 2 years later. Remarkably, the AVM draining vein decreased in diameter; at the 2-year follow-up MR imaging examination it was no longer visible. The nidus volume decreased to

Abbreviations used in this paper: ARE = adverse radiation effect; AVM = arteriovenous malformation; CT = computerized tomography; DW = diffusion-weighted; FLAIR = fluid attenuated-inversion recovery; GKS = Gamma Knife surgery; MR = magnetic resonance.

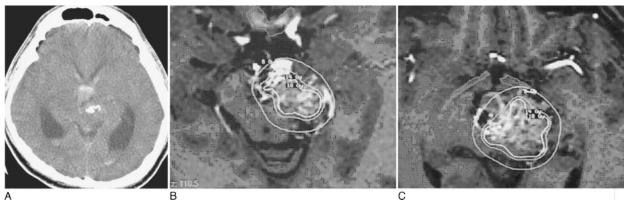


FIG. 1. A: A CT scan of the brain obtained in a previously healthy 20-year-old man after sudden onset of unconsciousness, revealing an intraventricular hemorrhage with calcified spots in the left midbrain. B and C: Cerebral angiography revealing an AVM in the left thalamus extending to the tegmentum (Spetzler–Martin Grade V).

less than that before GKS. These findings were compatible with the patient's clinical course.

Discussion

Midbrain AVMs constitute only between 4.3 and 11% of all AVMs;⁴ however, they represent a serious life- and function-threatening condition with an annual rebleeding risk of 9.8% after detection. This rebleeding rate is much higher than that for AVMs in other locations (2–4%/year).⁴Because of the location and the proximity of these AVMs to vital structures, the morbidity rate is significant, with 85.5% of patients suffering hemiparesis or hemiplegia if untreated.^{4,5} Therefore, aggressive

treatment is needed even if the treatment carries some risk.

Microsurgery offers the option of complete removal of an AVM in a single session; however, resection of midbrain AVMs is challenging.^{5,14} In the largest series reported in Japan, total removal of the AVM was achieved in only 56% of patients, and the rate of permanent deficits was 25%.¹¹ Endovascular embolization alone has not yet proven to be effective, serving primarily as an adjunctive treatment with radiosurgery or surgery of medium to large AVMs.^{5,9,14} Haw, et al.,⁸ reported on 513 procedures in 306 patients treated at the University of Toronto. They achieved only a 31% cure rate in a subgroup of 55 AVMs in which the goal was curative. There were 62 complications

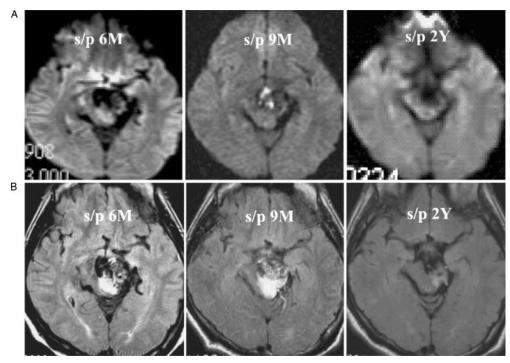


FIG. 2. Serial follow-up MR images obtained 3 months, 9 months, and 2 years post-GKS. Notably, a very small hyperintense lesion can be clearly identified in the left tegmentum caudomediodorsal to the left red nucleus on DW (A) and FLAIR (B) images. This ischemic spot enlarged 9 months after GKS, but became a blur 2 years later. The AVM draining vein is relatively less prominent and is no longer visible on the 2-year-follow-up images.

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in 56 patients. Notably, the rate of combined mortality and permanent neurological morbidity was 7.5% per patient.

At present, image-guided radiosurgery is widely accepted as an important therapeutic modality for the treatment of small- and medium-sized deep-seated AVMs, particularly if embolization is judged to be too difficult or dangerous.^{5,14} Our patient harbored a Grade V AVM with a deep-seated draining vein, making him a good candidate for GKS. Obliteration rates depend on the margin dose of radiation and the location and volume of the AVM nidus.^{5,14} For midbrain AVMs, the actuarial obliteration rates confirmed on angiography have been reported in nearly two-thirds of patients within 3 years.^{10,12} Radiosurgery performed in the brainstem poses significant (nearly 20% within 5 years) risks for radiation damage because of its compact critical pathways and multiple cranial nerve nuclei.^{10,12}

According to the Movement Disorders Society's consensus statement,² Holmes tremor is defined as a rest and intention tremor of low frequency, generally below 4.5 Hz, which is usually refractory to medical therapy. The onset of tremor after midbrain injury may be delayed and the delay has been known to range between 2 weeks and 2 years; this range has been applicable to injuries in the brainstem, cerebellum, and thalamus.³ The underlying neuropathological origins vary considerably and include hemorrhage, ischemia, trauma, neoplasm, metabolic disorders, and infections. Based on pathoanatomical and positron emission tomography studies, the nigrostriatal dopaminergic system and the cerebellothalamic system must be lesioned.³

Both DW imaging^{7,13} and cerebrospinal fluid suppressed–FLAIR¹ sequences are highly sensitive and specific techniques used in the early diagnosis of acute cerebral ischemia. Magnetic resonance DW imaging can detect vascular anomalies smaller than 1 mm in diameter.⁷ The area of hyperintensity demonstrated on serial DW imaging may remain for months or, in some cases, indefinitely. If it evolves into a hypo- or isodense area, this is often an indication that the underlying infarcted tissues may already have been repaired by reperfusion.¹³

Although this patient was relatively healthy even after a hemorrhagic midbrain stroke 1 year previously, symptomatic tremor appeared 2 weeks after GKS for an AVM. Clinically, the patient was healthy without any evidence of radiation-induced hemorrhage at this time. Regular follow-up MR imaging persistently demonstrated a small, hyperintense lesion caudomediodorsal to the left red nucleus. In theory, the cerebellonigrostriatal dopaminergic system should have been lesioned after GKS. The ischemic spot became more prominent 9 months after GKS, but had faded away by 2-year follow up, and the AVM draining vein became invisible. These radiological findings correlated well to the patient's clinical course of an initial deterioration and later remission.

Therefore, we strongly suppose that GKS can induce focal edema or infarction from inadvertent obliteration of penetrating arteries or vessels en passage. This alteration of regional blood flow, which might be asymptomatic in patients with AVMs of the cerebral cortex or white matter, can disrupt the cerebellorubrothalamic circuitry and induce the genesis of tremor.

Conclusions

Holmes tremor is a rare ARE after GKS; however, patients with midbrain AVMs should be advised of the possibility of its occurrence.

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