Arteriovenous malformation presenting with epilepsy: a multimodal approach to diagnosis and treatment

Sauson Soldozy, BA, Pedro Norat, MD, Kaan Yağmurlu, MD, Jennifer D. Sokolowski, MD, PhD, Khadijeh A. Sharifi, PhD, Petr Tvrđik, PhD, Min S. Park, MD, and M. Yashar S. Kalani, MD, PhD

Department of Neurological Surgery, University of Virginia Health System, Charlottesville, Virginia

Arteriovenous malformation (AVM) presenting with epilepsy significantly impacts patient quality of life, and it should be considered very much a seizure disorder. Although hemorrhage prevention is the primary treatment aim of AVM surgery, seizure control should also be at the forefront of therapeutic management. Several hemodynamic and morphological characteristics of AVM have been identified to be associated with seizure presentation. This includes increased AVM flow, presence of long pial draining vein, venous outflow obstruction, and frontotemporal location, among other aspects. With the advent of high-throughput image processing and quantification methods, new radiographic attributes of AVM-related epilepsy have been identified. With respect to therapy, several treatment approaches are available, including conservative management or interventional modalities; this includes microsurgery, radiosurgery, and embolization or a combination thereof. Many studies, especially in the domain of microsurgery and radiosurgery, evaluate both techniques with respect to seizure outcomes. The advantage of microsurgery lies in superior AVM obliteration rates and swift seizure response. In addition, by incorporating electrophysiological monitoring during AVM resection, adjacent or even remote epileptogenic foci can be identified, leading to extended lesionectomy and improved seizure control. Radiosurgery, despite resulting in reduced AVM obliteration and prolonged time to seizure freedom, avoids the risks of surgery altogether and may provide seizure control through various antiepileptic mechanisms. Embolization continues to be used as an adjuvant for both microsurgery and radiosurgery. In this study, the authors review the latest imaging techniques in characterizing AVM-related epilepsy, in addition to reviewing each treatment modality.

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ARTERIOVENOUS malformations (AVMs) are the result of abnormal shunting between high-flow arterial vessels and low-flow venous capacitance vessels, forming a dysplastic vascular nidus within brain parenchyma. The inherent flow disturbances within AVMs predispose lesions to rupture, and this occurs in nearly half of patients.²⁹ The second most common presentation of AVM is seizures, which occur in 20%–45% of patients.^{16,29} The mechanism of seizure in AVM is multifold, including those seizures directly due to hemorrhage and hemosiderosis, as well as seizures secondary to vascular steal, perinidal edema, and nidus size and location.^{16,17,29,55} Patient factors including male sex and age younger than 65 years have also been associated with seizure onset.²² In those who present

with seizure, at least half of patients with AVM will experience seizure recurrence within 5 years of a first-ever seizure event.²⁶ Comparing patients with focal hemorrhage with those who have unruptured AVMs, it is unclear, given conflicting reports, if greater seizure risk is conferred.^{12,26} Although the definition of epilepsy may take on different forms, patients experiencing seizure in the setting of a structural lesion qualify for a diagnosis of epilepsy according to the International League Against Epilepsy.¹⁸ Despite this working definition, patient outcomes vary depending on if they present with a first-ever seizure or with chronic or drug-resistant epilepsy (DRE).¹⁶

In this review the authors provide an overview of AVM-related epilepsy characterization and treatment, emphasizing

ABBREVIATIONS A-Vt = arterial-to-venous time; AED = antiepileptic drug; ARUBA = A Randomized Trial of Unruptured Brain Arteriovenous Malformations; AVM = arteriovenous malformation; DRE = drug-resistant epilepsy; ECoG = electrocorticography; EEG = electroencephalography; SRS = stereotactic radiosurgery.

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ing new technological advances in AVM-related epilepsy diagnostics. In addition, the findings of studies exploring single or combined embolization, radiosurgical, or microsurgical approaches are discussed in the context of seizure freedom.

Diagnostics and Imaging

Efforts have been made to radiographically distinguish nonepileptogenic AVMs from those that induce epilepsy, with cortical location being the most agreed-upon predictor of seizure activity.^{10,16,49,55} In a recent multicenter study including 2333 patients with AVM by Chen et al.,⁹ cortical AVM location was found to be the strongest predictor of seizure location (OR 1559.42, 95% CI 206.80–11,759.23; $p < 0.001$), with cortical AVMs constituting a seizure incidence of 27% (417/1525), whereas the noncortical AVM seizure incidence was 0.3% (3/800). Interestingly, a smaller nidus size was found to be associated with seizure risk in this study.⁹ The inconsistency in the reported association between AVM size and seizure risk may be due in part to age discrepancy at diagnosis, with increased age being associated with both smaller nidus size and increased seizure incidence.⁴⁵ Reports of prior hemorrhage conferring increased seizure risk are also conflicting.^{9,12,16,22,26} This leaves location as the most reliable predictor of seizure; in particular, a frontotemporal AVM location is more predictive of seizure than a presence in other cortical regions.⁵⁴ Despite this, whole lobar location alone remains nonspecific and is therefore an insufficient radiographic marker, although it remains a commonly reported metric in AVM-related epilepsy studies. With recent developments in hemodynamic quantification techniques and postprocessing tools in angiography and MRI, respectively, AVM-related epilepsy morphology and anatomical characteristics may be better characterized.

Angiography

The use of DSA in predicting AVM-related seizures has been demonstrated. Previous studies have reported several angioarchitectural predictors of seizure, including superficial venous drainage, superficial location with external carotid artery or middle cerebral artery feeding, and presence of venous ectasia.^{10,17,19,49} Searching for morphological features characteristic of AVM-related epilepsy, Fierstra et al.¹⁷ identified venous congestion in all patients with seizures ($n = 10$). Moderate to significant arterial dilation and even flow-related aneurysms were also noted in the seizure cohort, suggesting that high-flow shunting may impart enough wall shear stress to initiate aneurysm formation, further contributing to AVM-associated epilepsy.^{6,29,44} Shakur et al.⁴¹ also identified mean AVM flow to be significantly higher in patients with seizures ($p < 0.001$), with the presence of intranidal fistula, venous ectasia, and venous varix being associated with higher flow.

Given that evidence points toward AVM flow as being a contributing factor to AVM-related seizure, a scoring system based on AVM angioarchitecture was proposed by Shankar et al.⁴² Stratifying 78 patients with unruptured AVMs based on seizure presentation, the scoring system is based on the 3 strongest predictors of seizure: location,

venous outflow stenosis, and presence of long pial draining vein. Each component is given a score of 1, with a total score of 3 having high specificity (98%). Receiver operating characteristic curve analysis for the scoring system demonstrated good predictability and diagnostic performance (area under the curve 0.841, 95% CI 0.749–0.933).⁴²

Shakur et al.⁴⁰ sought to validate AVM flow obtained by DSA with true flow measurements from quantitative MRA. This ensures accurate interpretation of flow without reliance on time-to-peak analysis, which has been shown to be confounded by several factors, including catheter location during injection, amount of contrast injected, and vessel diameter. Using the cavernous segment of the ipsilateral internal carotid artery and draining veins closest to the AVM nidus as regions of interest, contrast time-density analysis was performed to determine the difference in peak contrast intensity between these 2 regions of interest on DSA imaging. This metric was denoted arterial-to-venous time (A-Vt), with reduced A-Vt corresponding to increased shunting. The transit time of DSA contrast to the AVM draining vein was also determined using the postprocessing software syngo iFlow (Siemens Healthineers).^{31,47} Both A-Vt ($r = -0.47$, $p = 0.01$) and iFlow transit time ($r = -0.44$, $p = 0.01$) methods correlated with AVM flow as determined by quantitative MRA, suggesting that both DSA-dependent measures accurately estimate and reflect true AVM flow. However, significantly shorter iFlow transit time ($p = 0.02$) alone and not A-Vt ($p = 0.68$) was observed in patients with seizures, corresponding to significantly greater AVM flow times in this cohort ($p = 0.02$).⁴⁰ Given that patients with ruptured AVM and seizure were not mutually exclusive in this study, it is possible that the presence of hemorrhage alters A-Vt and iFlow measurements differently based on the quantification technique used. For this reason, stratifying unruptured AVMs from those presenting with hemorrhage may prove useful in further validating these estimates of AVM flow.

Magnetic Resonance Imaging

Recent MRI studies have been used to explore MR characteristics of unruptured AVMs, with seizure as an initial clinical presentation. For instance, Benson et al.³ retrospectively reviewed 165 patients with unruptured AVMs, 57 of whom presented with seizures. Perinidal edema (OR 4.67, 95% CI 2.08–10.45; $p < 0.0001$); perinidal T2* blooming (OR 4.31, 95% CI 1.20–15.46; $p = 0.029$); venous pouch/varix (OR 3.46, 95% CI 1.77–6.77; $p = 0.0003$); long draining vein (OR 8.32, 95% CI 3.08–22.46; $p < 0.0001$); and larger size based on Spetzler-Martin grading (OR 2.49, 95% CI 1.28–4.82; $p = 0.006$) were significantly associated with initial seizure presentation. These findings are mostly in agreement with the described angiography studies.^{17,40,42} Nevertheless, despite the fact that the presence of perinidal brain edema is often associated with partial venous outlet thrombosis, which in turn may lead to neurological deficits and seizures,²⁹ thrombosed venous pouch was not found to be associated with seizure presentation in this study.¹⁶ Additionally, in spite of the results from angiography studies, the presence of neither intranidal nor feeding artery aneurysm was found

to be statistically different between the seizure and non-seizure group.^{16,17,40,42} With respect to AVM location, only frontal lobe (OR 2.74, 95% CI 1.42–5.33; $p = 0.004$); motor cortex (OR 4.07, 95% CI 1.76–9.40; $p = 0.001$); and sensory cortex (OR 3.5, 95% CI 1.45–8.42; $p = 0.006$) were associated with seizures.

In an attempt to better characterize and quantify exact AVM-related epileptogenic brain regions, Zhang et al.⁵⁵ used atlas-based analysis and radiomics to explore imaging data at the voxel level. Radiomics is a newly emerging translational field of medicine that refers to the extraction of quantitative imaging parameters that are believed to correlate with pathophysiological aspects of the tissue being examined.³⁹ Radiomics has already been demonstrated in tumor-related epilepsy, but this is the first study of its kind to use that modality in AVM-related epilepsy surgery.^{32,54} Of the brain regions identified, the occurrence of epilepsy was significantly associated with the proportion of damage to the right precentral gyrus and right superior longitudinal fasciculus. Combining these 2 locations with 4 radiomics features, a model was developed with a high predictive accuracy (area under the curve 0.866, 95% CI 0.791–0.940). It was found that increasingly heterogeneous AVMs were more prone to seizure, although the study did not correlate radiomics features with qualitative AVM angioarchitecture. In addition, the study did not include perinidal areas for analysis, failing to account for gliosis or vascular steal-induced epilepsy of nearby brain structures.^{17,29,55}

Treatment Approaches

There are several avenues one can take when addressing AVM-related epilepsy. Often, in unruptured AVMs medical management alone with anticonvulsant therapy is pursued initially, with pharmacoresistant epilepsy prompting further intervention. The International League Against Epilepsy defines DRE as being medically refractory to 2 trials of antiepileptic drugs (AEDs), resulting in failure to sustain seizure freedom.²⁸ Should anticonvulsant therapy fail to achieve seizure control, radiosurgery, endovascular embolization, microsurgical resection, or a combination thereof may be pursued. The effects of different treatment modalities on hemodynamics have been demonstrated in AVM,¹⁶ which may serve to explain the differences in seizure control with respect to treatment approach.

A meta-analysis composed of 24 studies totaling 1157 patients concluded that seizure control for AVM-related epilepsy was directly related to attaining complete AVM obliteration, with total obliteration being more likely with microsurgery. Therefore, microsurgery was concluded to have the greatest seizure control among the other approaches.² Another meta-analysis published 2 years later concluded that neither interventional therapy nor medical management alone is superior in achieving seizure freedom, providing further conflicting data in an already obscure treatment arena.²⁷

Medical Management

AVM-related epilepsy appears to be somewhat controlled with medical management alone, with routine pre-

scription of AEDs being generally advised in these patients. In a study by Josephson et al.,²⁶ 43 patients with AVM without a history of hemorrhage or functional neurological deficit who either presented with or had developed epilepsy on 5-year follow-up had a 45% chance of achieving 2-year seizure freedom. This was despite the fact that 91% (39/43) of patients with AVM-related epilepsy were receiving AEDs, with 46% (16/35) of patients receiving polytherapy by the end of the follow-up period. Another study by Stephen et al.⁴⁶ reported greater seizure control, with 78% (11/14) of patients with AVM being seizure free for at least 1 year prior to the last follow-up visit. Among the patients with AVM who attained adequate seizure control, 64% only required 1 AED.

Recently, A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA) published findings comparing medical management alone to medical management combined with interventional therapy.³⁵ ARUBA is a multicenter, nonblinded, randomized trial that recruited 223 patients with unruptured brain AVMs; 109 were assigned to medical management and 114 were assigned to interventional therapy. Although the primary endpoint of ARUBA is time to death or symptomatic stroke, data with respect to seizure presentation were also presented. Among the medical management cohort, 41% (45/109 patients) presented with seizure, which was comparable to the interventional therapy group at 44% (50/114). At a mean follow-up of 33.3 months, 37% (40/109) of patients continued to experience seizure, compared to 44% (50/114) in the interventional group ($p = 0.34$). The rates of seizure per patient-year were comparable, at 0.131 for the medical management group and 0.160 for the interventional group.³⁵ These findings suggest that regardless of treatment approach, AVM-related epilepsy continues to persist—although care should be taken when interpreting these results because heterogeneity of patients, lack of standardization of the treatment arm, and short follow-up are among the critiques and limitations of ARUBA.³⁴ Additionally, several single-center and multicenter studies have shown favorable outcomes in ARUBA-eligible patients undergoing intervention, further challenging the findings of ARUBA.^{11,43,51}

Microsurgery

The role of microsurgery in treating AVM-related epilepsy continues to be debated, although recent series demonstrate positive seizure control. A study by Englot et al.¹⁵ evaluated seizure outcomes in 440 patients who underwent microsurgery for supratentorial AVMs at a single center. In that study, 222 patients (50%) received preoperative embolization, with 21 patients (5%) having undergone radiosurgery prior to resection. A total of 23 patients (5%) progressed to DRE. After microsurgical resection, 93% of patients who presented with preoperative seizure exhibited a modified Engel class I outcome on follow-up (mean 20.7 months), characterized by complete seizure freedom or only a single occurrence after surgery. Of the 23 patients with DRE, 21 (91%) demonstrated a positive postoperative course. A 3% incidence of new postoperative seizure was reported in patients without preoperative seizures, which is lower than reported in the literature.^{15,16,21}

Another study including 103 surgically treated patients presenting with seizure demonstrated seizure freedom rates of 77%, 79%, and 84% at 1-, 2-, and 10-year follow-up.¹⁶ These seizure freedom rates are consistent with other surgical series.^{2,16,21,37,52} When stratifying patients based on seizure presentation (sporadic seizure, chronic epilepsy/several seizures, and DRE), the authors found that patients with DRE ($n = 24$) have the worst outcomes. Several patients ($n = 13$) had further epileptological workup, including electroencephalography (EEG) and intraoperative electrocorticography (ECoG), leading to additional hippocampectomy in 30.8% (4/13) of patients and extended lesionectomies in 38.5% (5/13) of patients. Two other DRE cases had additional temporomesial resection without additional epilepsy surgery workup. Overall, greater seizure freedom was achieved in patients with DRE in whom extended lesionectomy (75%) was performed when compared to patients with DRE undergoing standard AVM resection alone (52.9%), although this difference did not reach statistical significance given the small sample size of patients in these categories.¹⁶

The use of EEG and intraoperative ECoG for AVM surgery presenting with epilepsy appears promising but has been reported sparingly. Prior studies suggest implementing these tools for AVM-related epilepsy to identify and remove epileptic foci caused by secondary epileptogenesis.^{4,7,52} Yeh et al.⁵² used preoperative EEG and intraoperative ECoG in a study of 54 patients with AVM-associated epilepsy (mean follow-up 4.8 years). Cortical excision was performed in 46.3% (25/54) of patients. Epileptic cortex adjacent to the AVM was excised in 56% (14/25) of patients, temporomesial resection in 36% (9/25) of patients, with 8% (2/25) of other patients requiring second procedures for excision of remote seizure foci. On follow-up, 70.4% (38/54) of patients experienced excellent outcomes, defined as being seizure free or experiencing occasional auras. Of the 25 patients requiring extended lesionectomies, 64% (16/25) were among those who became seizure free after surgery. These findings suggest that EEG and ECoG may be useful in surgical planning and improving seizure control, especially in patients with AVM-associated DRE. This was further demonstrated by Cao et al.,⁴ who incorporated intraoperative ECoG-guided bipolar electrocoagulation in a series of 60 patients with AVM presenting with seizure. Forty-nine (81.7%) patients were found to have epileptic discharges before and after AVM resection and therefore underwent bipolar electrocoagulation of spike-positive cortex. This relieved epileptic discharge in 45 patients, with the remaining 4 having diminished signal. On follow-up (mean 4.3 years) in 55 patients, 39 (70.9%) were class I, 7 (12.7%) were class II, 5 (9.0%) were class III, and 4 (7.2%) were class IV on the Engel seizure outcome scale.

Radiosurgery

Radiotherapy began to emerge as a treatment option for both tumors and AVMs in the late 1980s,¹ with Heikkinen and colleagues publishing one of the first series to demonstrate seizure resolution in patients with AVM-related epilepsy treated with stereotactic proton beam irradiation.²⁰ Since then, radiosurgical techniques have been refined

and demonstrated as a safe alternative to microsurgery and embolization for achieving seizure obliteration.^{9,14,24,36}

In a meta-analysis including 137 observational studies totaling 13,698 patients, van Beijnum et al.⁵⁰ concluded that stereotactic radiosurgery (SRS) achieved the lowest case-fatality rate—0.5 (95% CI 0.43–0.58) per 100 person-years, compared to 1.1 (95% CI 0.87–1.3) after microsurgery and 0.96 (95% CI 0.67–1.4) after embolization. In addition, complication rates were lowest for SRS (5.1%), compared to 7.4% and 6.6% for microsurgery and embolization, respectively. However, given an obliteration rate of 38% for SRS compared to 96% in microsurgery, the question remains regarding the effectiveness of SRS in achieving adequate seizure control.

Several series have been published that report seizure outcomes following SRS for AVM-related epilepsy.^{8,9,12–14,24,36,38} Recently, Ironside et al.²⁴ published a meta-analysis that reported seizure outcomes in a total of 4826 patients across 27 studies who underwent SRS for AVM-associated seizures. Seizure control (seizure freedom or seizure improvement) was achieved in 910 of 1312 patients (random-effects model, 73.1% [95% CI 66.9%–78.9%]), with complete seizure freedom being achieved in 597 of 1245 patients (random-effects model, 55.7% [95% CI 44.5%–66.6%]). Seizure status remained unchanged in 219 of 914 patients (random-effects model, 18.7% [95% CI 12.4%–26.0%]) and worsened in 39 of 675 patients (random-effects model, 6.1% [95% CI 3.3%–9.7%]).²⁴ This rate of seizure control is comparable to those reported by surgical series,^{2,16,21,37,52} with the exception of 1 study, which reported a modified Engel class I outcome in 93% of patients.¹⁵ With de novo seizures in 89 of 2006 patients (random-effects model, 5.2% [2.4%–8.9%]), this value is also comparable to the published surgical literature, except for a single study that reported a 3% incidence of de novo seizures.^{15,16,21}

Ironside et al.²⁴ also identified generalized seizure type (OR 2.30, 95% CI 1.26–4.20; $p = 0.01$); history of ≤ 5 seizures (OR 6.80, 95% CI 3.37–13.73; $p < 0.001$); previous AVM hemorrhage (OR 4.83, 95% CI 2.19–10.67; $p < 0.001$); and complete AVM obliteration (OR 4.61, 95% CI 2.33–9.22; $p < 0.001$) as statistically significant predictors of seizure freedom. Using the random-effects model in the meta-analysis, 75.1% (330/450) of patients with complete obliteration achieved seizure freedom, compared to 42.5% (145/321) without obliteration. It should be noted that previous embolization in 107 of 526 patients (13.5%) and microsurgery in 28 of 440 patients (6.7%) was performed prior to SRS. Hung et al., however, recently demonstrated that the rates of obliteration and favorable outcome of patients who underwent embolization before SRS were comparable to those who underwent SRS without preembolization.²³

The higher likelihood of seizure control with complete obliteration found in this study confirms the findings of an earlier meta-analysis by Baranoski et al.² However, it has been previously reported that SRS, when compared to microsurgery, has lower AVM obliteration rates,⁵⁰ raising the question of how SRS is able to achieve seizure control with suboptimal AVM eradication. This suggests that SRS for AVM-related epilepsy imparts mechanisms besides obliteration for seizure control.

Several antiepileptic mechanisms specific to radiosurgery have been explored. This includes neuromodulation of perinidal brain parenchyma, including formation of a protective gliotic capsule, ischemic changes at the nidus, and reduction of vascular steal.^{24,30,33} These mechanisms may be related to the secondary parenchymal changes that occur in the setting of radiosurgery, and they appear to be dose related.⁵ For instance, a diffusion tensor imaging study has detected wallerian degeneration in nerve fiber tracts adjacent to the AVM site in a patient treated with radiosurgery.⁵³ In a histopathological study, Tu et al. demonstrated that radiotherapy imparts irreversible damage to endothelial cells and induces contraction in myofibroblasts adjacent to the elastic layer of AVM vessel walls.⁴⁸ This contraction narrows the vessel lumen, contributing to vaso-occlusion. Additionally, smooth-muscle cell neoproliferation was shown to further induce stenosis in both AVM vessels and adjacent feeders, subsequently giving rise to ischemic changes that may contribute to an altered seizure profile in patients.

Embolization

Embolization as an independent treatment modality has been studied sparingly, although it continues to be primarily used as an adjunct to both microsurgery and radiosurgery. Zhang et al.⁵⁴ sought to evaluate seizure control in patients after ethylene vinyl alcohol (Onyx) embolization. Of the 68 patients with AVM presenting with seizure, 19 were treated endovascularly alone, and 18 were treated with combined embolization and Gamma Knife surgery. Complete AVM obliteration and seizure freedom were both achieved in 51.4% (19/37) of patients (mean follow-up 31.2 months). Seizure freedom rates were higher in patients with complete embolization (57.9%) when compared to partial embolization (44.4%).

Lv et al.³³ also reported their outcomes following the endovascular treatment of 30 patients with AVM-related seizures. Complete AVM obliteration was achieved in 4 patients, with 18 patients becoming seizure free after a single embolization, 2 patients becoming seizure free after a second embolization, and 1 patient after a third embolization, for an overall seizure freedom rate of 70% (21/30).³³

It is believed that AVM embolization provides its benefit on seizure control by rendering epileptogenic brain tissue hypoxic, although this may induce intranidal angiogenesis and thus seizure recurrence.^{25,33,54} Notwithstanding, patients treated solely with embolization who continue to experience seizures probably harbor residual gliotic plaques and perinidal gliosis, in addition to epileptic foci distal from the primary AVM site.^{33,54}

Conclusions

There is agreement between studies that cortical location, features of high flow, and evidence of venous congestion are associated with seizure presentation.^{4,29,40,42} Given that AVMs with middle cerebral artery feeders are more associated with seizures, this may also serve to explain why AVMs within the frontotemporal cortex are epileptogenic.^{29,42} The use of more sophisticated MRI postprocess-

ing and angiographic quantification can serve to better characterize epileptogenic AVMs and guide future treatment strategies,^{40,42,55} although further studies with larger sample sizes and predetermined angiographic parameters are necessary to draw conclusions on the use of AVM morphology in predicting epileptogenicity.

Although it remains unclear whether medical management alone may sufficiently treat AVM-related epilepsy, existing evidence suggests moderate to low effectiveness. Despite the findings of ARUBA, several studies have since emerged challenging its generalizability. In addition, the safety of interventional therapy has been well established, with SRS proving to be safer than microsurgery and embolization.⁵⁰ However, the selection and combination of treatment modalities should be determined on a case-by-case basis given the heterogeneity of AVM-related epilepsy. Depending on the severity and history of seizure presentation, one treatment approach may be best suited, which is especially true if one is considering time to seizure-free status as a factor in patient quality of life posttreatment.¹⁶ In addition, practitioners may consider greater implementation of EEG and intraoperative ECoG, because this may help identify additional adjacent or remote epileptic foci for further lesionectomy that would otherwise not be addressed. AVM-related epilepsy remains a complex disease process, requiring improved characterization and more standardized treatment protocols.

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Disclosures

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

Conception and design: Kalani, Soldozy. Acquisition of data: Soldozy. Analysis and interpretation of data: Soldozy. Drafting the article: Soldozy. Critically revising the article: Soldozy, Norat, Yağmurlu, Sokolowski, Sharifi. Approved the final version of the manuscript on behalf of all authors: Kalani. Administrative/technical/material support: Kalani, Norat, Yağmurlu, Sokolowski, Sharifi, Tvrdik, Park. Study supervision: Kalani, Tvrdik, Park.

Correspondence

M. Yashar S. Kalani: University of Virginia Health System, Charlottesville, VA. stemcelldoctor@gmail.com.