Intracranial Vascular Malformations and Epilepsy

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Abstract

Among the spectrum of intracranial vascular malformations (IVMs), arteriovenous malformations (AVMs), and cavernous malformations (CCMs) are of particular importance for epilepsy. Seizures are a common mode of presentation for both conditions. Seizures may occur de novo or secondary to intracerebral hemorrhage. Timely imaging is thus crucial for patients with seizures and AVMs or CCMs. Patients with a first-ever AVM- or CCM-related seizure can now be considered to have epilepsy according to the International League Against Epilepsy criteria. Observational studies and case series suggest that between 45 to 78% of patients with AVM-related epilepsy and 47 to 60% of patients with CCM-related epilepsy may achieve seizure freedom through antiepileptic drugs (AEDs) alone. Invasive procedures are available although current evidence suggests that epilepsy-specific preintervention evaluations are underused. Randomized controlled trials and population-based studies have demonstrated worse short-term functional outcomes after routine intervention on unruptured AVMs or CCMs when compared with conservative management. The role of invasive therapy for IVM-related epilepsy has yielded mixed results. Case series have reported high estimates of seizure freedom although these results have not been replicated in controlled observational studies. Randomized controlled trials of immediate invasive therapy versus conservative management, in addition to usual care with AEDs and of different types of treatment and their timing, are warranted for AVMs and CCM-related epilepsy.

Keywords
► arteriovenous malformations
► cavernous malformations
► epilepsy
► antiepileptic drugs
► epilepsy surgery

Intracranial vascular malformations (IVMs) encompass a spectrum of blood vessel abnormalities that are of clinical importance because they may cause epileptic seizures and/or hemorrhage. In this narrative review, we will focus on brain arteriovenous malformations (AVMs) and cerebral cavernous malformations (CCMs) because they are the IVMs mainly responsible for epileptic seizures.

Arteriovenous malformations are abnormal tangles of dilated arteries and veins of varying caliber lacking an intervening capillary network, which results in direct arteriovenous shunting from the high-pressure arterial system to the low-pressure venous system. This in turn dilates to form a tangled nidus (Latin nidus, nest). The prevalence of asymptomatic AVMs is approximately 1 in 2000 (0.05%). The symptomatic AVM detection rate is 0.89 (95% confidence interval [CI] 0.70–1.12) per 100,000 adults per year, split roughly 2:1 between hemorrhage versus epileptic seizure(s).2,3

Cerebral cavernous malformations are sinusoidal vascular channels devoid of muscular and elastic tissue, lined by a single layer of endothelial cells that lack intervening tight junctions; they are distinguished from capillary telangiectasias by the absence of neural parenchyma within the
malformation. The prevalence of asymptomatic CCMs is approximately 1 in 625 (0.16%). The symptomatic CCM detection rate is one-third to one-quarter that of AVMs, 0.24 (95% CI 0.15–0.38) per 100,000 adults per year, again split roughly 2:1 between hemorrhagic or nonhemorrhagic focal neurologic deficit(s) versus epileptic seizure(s).

Although there is no evidence that AVM detection rates have increased over time, indirect comparisons between the populations in Scotland 1999 to 2000 and Olmsted County Minnesota 1965 to 1992 confirm that CCM detection has increased over time. This is possibly due to the increasing use of magnetic resonance imaging (MRI), which is especially likely to be the case among patients with epilepsy who are routinely imaged with brain MRI now, but less so in the past.

AVMs and CCMs as a Cause of Seizures

Epileptic seizures are a frequent manifestation of AVMs and CCMs. However, because a hemorrhage from an AVM or CCM can present with a seizure alone, it is crucial that timely imaging with the correct modality establishes whether hemorrhage has occurred. Correctly defining the mode of presentation is a critically important step because this carries prognostic and therapeutic implications for the patient: The risk of future hemorrhage is higher if a patient with an AVM or CCM has presented with hemorrhage than if they presented without.

Because epileptologists see a disproportionate number of patients with intractable epilepsy in comparison to other neurologists, we often fear the clinical course of epilepsy related to AVMs and CCMs. In this article, we will try to give the broadest perspective possible by summarizing data about patients with AVMs and CCMs concerning the risk of epilepsy occurred.

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Pathogenesis of Seizures and Epilepsy

The Pathology of Epileptogenesis

Epileptogenesis is the development and extension of tissue that is capable of generating spontaneous seizures. This includes development of an epilepsy condition and progression after the condition is established. The epileptogenic zone is the area of brain that is both necessary and sufficient for the generation of epileptic seizures. Removal or disconnection of this region is necessary to achieve seizure freedom. The ictal onset zone refers to the cortical region from which we can objectively demonstrate that seizures originate. The ictal onset and epileptogenic zones do not necessarily overlap. Patients with a mirror focus may be rendered seizure free through removal of an epileptogenic lesion that constitutes the entire epileptogenic zone. The irritative zone is the area of the cortex that generates interictal spikes.

Mapping the IVM’s position within this network is critical because understanding seizure pathogenesis may influence how epilepsy surgery is planned. For instance, the IVM may exist as an epileptogenic lesion, whereby a simple lesionectomy would be expected to yield complete seizure freedom. Alternatively, it may function as a constituent, such as an ictal onset zone, within a larger epileptogenic zone wherein an extended resection would be required for seizure freedom.

Specific Pathogenic Mechanisms

In general, epileptic seizures originate from zones of cell loss rather than from the more normal appearing adjacent cortex. This suggests that lesions causing incomplete damage, patchy cell loss, and sclerosis, rather than complete parenchymal destruction, may result in secondary synaptic reorganization, hypersynchrony, and hyperexcitability.

Intracranial vascular malformations, potentially as mass lesions and certainly through hemosiderin deposition, can cause chronic irritation and remodeling of the underlying cerebral cortex. Thus, as long as there is sufficient residual parenchyma, the damaged but still functional cortex may reorganize itself into an epileptogenic network.

Arteriovenous malformations may cause sufficient cell damage to promote epileptogenic pathways through direct shunting of blood from the arterial to the venous compartment. This may lead to chronic ischemia and frank infarction. Impaired perinidal cerebrovascular reserve, not severe enough to result in vascular steal, but significant enough to cause venous congestion and impaired microvascular autoregulation, may additionally result in parenchymal irritation and seizures.

Subclinical hemorrhage or persistent hemosiderin deposition may contribute to chronic cortical irritation and gliosis.

Additional epileptogenic mechanisms play a prominent role in CCM-related epilepsy. Cerebral cavernous malformations seem to have a greater propensity to cause chronic epilepsy compared with other mass lesions. There is no evidence to suggest that CCMs have intrinsic epileptogenicity or that they exert an epileptogenic effect simply as space-occupying masses; instead, chronic hemosiderin deposition through leaky endothelial junctions may promote a chronic epilepsy state due to iron deposition and generation of free radicals. In this model of epilepsy, elevated concentrations of serine and glycine in the peripheral zones of CCMs and perilesional albumin leakage were suggested to promote hyperexcitability.

Occasionally, there is dual epileptogenic pathology in association with IVM-related epilepsy. The coexistence of IVMs and focal cortical dysplasia was deemed frequent enough to warrant its own category (FCD type IIc) in the 2011 International League Against Epilepsy classification scheme. Intracranial vascular malformations may also occur with other epileptogenic lesions, such as mesial temporal lobe sclerosis and glioneuronal tumors.

There are reports of rare instances in which patients with AVM-related epilepsy later developed semilogically different seizures from a distant seizure focus, while coincident mesiotemporal bursts and continuous spiking have been recorded using intraoperative electrocorticography in patients with CCM-related epilepsy. These reports provide some theoretical support for the potential benefit of early intensive treatment of IVM-related epilepsy; however, in general, attempts to establish truly “antiepileptogenic” strategies have so far proven unsuccessful.
Epidemiology and Risk Factors for Seizures and Epilepsy

Arteriovenous Malformations

Presentation Due to a Seizure

The median percentage of patients with AVMs presenting with a seizure in hospital-based studies is 30% (interquartile range [IQR] 22–35%)\(^{35-62}\); an inflated estimate compared with that reported in population-based studies, which by nature, are less prone to selection bias (median 14%; IQR 12–24%; \(\text{Fig. 1A}\)\(^{1,5,63-65}\)). Factors that have been associated with a seizure presentation include male sex,\(^{41,66}\) younger age,\(^{41,67}\) temporal\(^{3,41,60}\) or frontal\(^{60}\) AVM nidus location, an AVM nidus diameter > 3 cm,\(^{41,66}\) superficial or cortical location,\(^{60,66,68}\) middle cerebral artery feeders,\(^{68}\) an absence

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**Fig. 1** (A, B) Forest plot of the percentage of patients presenting with a seizure as the first manifestation of their arteriovenous malformation (A) or cerebral cavernous malformation (B), stratified by patient source (clinic or population-based). A formal meta-analysis was not possible due to significant statistical heterogeneity. Median proportions (including interquartile ranges; IQRs) presenting with a seizure are reported in lieu of a pooled estimate. CI, confidence interval.
of associated aneurysms,\textsuperscript{66,68} the presence of a venous varix/varices,\textsuperscript{66,68} and superficial venous drainage\textsuperscript{66} (\textit{Table 1}).

First-Ever Seizure
The 5-year prospective risk of a first-ever seizure is estimated to be 8\% (95\% CI 0–20\%) following presentation with an unruptured, incidentally discovered AVM.\textsuperscript{3} Patients with a prior intracerebral hemorrhage (ICH) or a focal neurologic deficit are at significantly higher risk,\textsuperscript{3,69} with an estimated 5-year risk of 23\% (95\% CI 9–37\%).\textsuperscript{3} The 5-year risk is particularly high for patients with acute symptomatic seizures secondary to ICH at the time of presentation (48\%; 95\% CI 19–77\%) and with temporal lobe AVMs (odds ratio [OR] 6.5; 95\% CI 1.8–23).\textsuperscript{3}

Epilepsy
Not all patients presenting with a first-ever seizure will subsequently develop epilepsy. The estimated 10- and 20-year risks of de novo epilepsy were 11\% and 18\%, respectively, according to a study of 343 patients diagnosed from 1941 to 1948.\textsuperscript{59} No patient presenting with a nonhemorrhagic focal neurologic deficit or an incidentally discovered AVM developed de novo epilepsy over this time frame.

More recent prospective, population-based data have estimated the 5-year risk of developing epilepsy following a first seizure attributed to an unruptured AVM to be 58\% (95\% CI 40–76\%).\textsuperscript{3} The risk of epilepsy may be higher for females,\textsuperscript{59} those with a younger age at AVM diagnosis,\textsuperscript{69} and those with a history of AVM surgery (57\% vs. 11\% 10-year risk, \( p < 0.001 \)).\textsuperscript{69}

Cerebral Cavernous Malformations
Presentation Due to a Seizure
The median percentage of patients with CCMs presenting with a seizure in hospital-based studies is 47\% (IQR 32–51\%); an estimate that is again inflated compared with that reported in a population-based study (25\%; 95\% CI 19–33\%; \textit{– Fig. 1B}).\textsuperscript{3} Factors associated with a seizure presentation in individual studies include male sex,\textsuperscript{83} multiple CCMs,\textsuperscript{3} supratentorial CCMs,\textsuperscript{82} superficial CCMs,\textsuperscript{82} and involvement of cerebral cortex\textsuperscript{90} (\textit{– Table 2}).
First-Ever Seizure
The annual risk of a first-ever CCM-related epileptic seizure has been imprecisely defined because of the paucity of patients with an incidentally detected CCM in cohort studies and the low event rate. One hospital-based study found this risk to be 2.4% per patient-year (95% CI unknown). The only population-based study found the 5-year risk from time of first diagnosis of an incidental, ruptured CCM was 4% (95% CI 0–10%), and this was not significantly higher following presentation with an intracerebral hemorrhage or focal neurologic deficit (6%, 95% CI 0–14%).

Epilepsy
The 5-year risk of developing epilepsy in patients with no history of ICH or a focal neurologic deficit has been estimated at 94% (95% CI 84–100%). This risk is significantly higher than that reported for AVMs ($p = 0.02$), and most of the events occur within the year following the initial seizure.

Investigations

Neuroimaging
The diagnosis of an IVM typically requires timely neuroimaging. A hemorrhage may initially be detected on computed tomography (CT). Suspicion of an AVM may be raised through identification of hyperdense serpentine vascular structures or nidal or vascular calcifications.

Magnetic resonance imaging permits anatomical localization of the AVM nidus, and may reveal parenchymal signatures of hemorrhage that can help identify whether an old symptomatic focal neurologic deficit was attributable to AVM-related intracerebral hemorrhage. Magnetic resonance imaging is the diagnostic modality of choice for detecting CCMs, which are traditionally considered to be “angiographically occult.” Repeated symptomatic and asymptomatic hemorrhage is a defining characteristic of CCMs. The ferromagnetic properties of the evolving process of hemosiderin deposition and calcification of the surrounding parenchyma results in heterogeneities of the local magnetic field that can be exploited by MRI to classify CCMs into four categories based on their appearance on T1- and T2-weighted conventional spin echo and gradient echo sequences.

Angiographic imaging (CT and MR angiography [MRA] and intra-arterial catheter digital subtraction angiography [IADSA]) can identify AVMs by demonstrating a nidus and early arteriovenous shunting. Although IADSA is traditionally considered the reference standard imaging modality for AVMs, CT and MRA appear comparable for identifying AVMs following intracerebral hemorrhage. Some form of angiography is prudent when an IVM is suspected on basic imaging to distinguish AVM from CCM.

Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) can be useful imaging tools for presurgical evaluations because they help to map ictal onset, and potentially, the epileptogenic zone. These forms of functional imaging have been used to limit complications from AVM resections, and their inclusion in

<table>
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<th>Study</th>
<th>Male</th>
<th>Younger age</th>
<th>Left-sided</th>
<th>Temporal lobe</th>
<th>Frontal lobe</th>
<th>AVM nidus</th>
<th>Nidus diameter &gt; 3 cm</th>
<th>Superficial or cortical location</th>
<th>Varix</th>
<th>Middle cerebral artery feeders</th>
<th>No associated aneurysm</th>
<th>Superficial venous drainage</th>
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<td>Galletti et al, 2014</td>
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<td>Turjman et al, 1995</td>
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* indicates the variable was associated with a seizure presentation in that particular study.
routine presurgical protocols for CCM-related epilepsy have been advocated.103 However, further research is warranted to help discern the expected changes in cerebral perfusion and metabolism attributable to the IVM from other abnormalities that may reliably define the ictal onset or epileptogenic zones.

**Video-Electroencephalography (Video-EEG) Monitoring**

Video-electroencephalography (EEG) monitoring may be useful if the diagnosis of epilepsy is uncertain, if an IVM is one of two or more potential structural causes of seizures, or if epilepsy surgery is planned.104 The patient’s usual seizures should be recorded and concurrent video and EEG data are used for surgical localization.105 Unfortunately, there are few data available to assess the impact of routine video-EEG on seizure-free outcomes in IVM-related epilepsy. This information would be valuable because routine presurgical workup incorporating video-EEG and standardized volumetric MRI sequences appears underused in IVM-related epilepsy106 and may reveal unanticipated dual pathology, such as hippocampal sclerosis or focal cortical dysplasia, or multiple CCMs.

**Treatment**

**Medical Management**

**Arteriovenous Malformations**

Patients with an unruptured AVM and a first-ever seizure now meet the new International League Against Epilepsy’s definition of epilepsy3,107 because their 5-year risk of a second seizure is 58% (95% CI 40–76%).3 The risk may be even higher for women and younger patients, so routine prescription of AEDs could be considered for this population. A population-based study found that the chance of achieving 2-year seizure freedom over 5 years of follow-up following a diagnosis of epilepsy (based on the occurrence of two or more seizures and no history of ICH or a focal neurologic deficit) was 45% (95% CI 20–70%); 91% of the patients studied were prescribed an AED.3 An older study found that patients with AVM-related epilepsy appeared to have a comparable, if not better, response to medical management than patients with other focal brain lesions, with up to 78% achieving 1-year seizure freedom.108

**Cerebral Cavernous Malformations**

Almost all patients with a CCM who suffer a first-ever seizure and have no history of ICH develop epilepsy. Hence, immediate AEDs after a first-ever CCM-related seizure appears justified and has been recommended by the ILAE task force.109 A population-based study found that the chance of achieving 2-year seizure freedom over 5 years of follow-up in conservatively managed patients with CCM-related epilepsy and no history of ICH (97% of whom were prescribed AEDs) was 47% (95% CI 27–67%),3 whereas studies from single institutions have found that up to 60% of patients can be well controlled on AEDs.110,111

**Interventional Management**

Vascular surgery, embolization, and radiosurgical procedures are conventionally used to reduce the future risk of hemorrhage conferred by vascular malformations. It has been assumed that by proxy these procedures may also have a positive impact on the patient’s epilepsy. However, the risk of seizures and epilepsy stems from fundamentally different processes than the risk of ICH. Pathological changes to the surrounding parenchyma and the extent of the epileptogenic zone exert a profound influence on the postoperative chances of achieving seizure freedom. It is imperative to resect or disconnect the epileptogenic zone completely to eradicate seizures. Hence, more extensive resections, rather than simple removal of the IVM, are frequently required to achieve acceptable rates of seizure freedom.

**Arteriovenous Malformations**

The annual risk of ICH from an unruptured AVM appears to be 1.3% (95% CI 1.0–1.7%), while that for ruptured AVMs is 4.8% (95% CI 3.9–5.9%) according to an individual patient data meta-analysis from four centers (n = 2525; 6,074 patient-years follow-up).311 In the ARUBA (A Randomized Trial of Unruptured Brain AVMs) randomized controlled trial and Scottish observational population-based study, medical management has been shown to be superior to AVM interventional therapy (neurosurgery, embolization, or stereotactic radiosurgery) for prevention of ICH and death in the short term.112,113 so enthusiasm for interventional management for unruptured AVMs may decline. These results need to be borne in mind when contemplating surgery to obliterate unruptured AVMs that have presented with epilepsy, although the long-term effects of interventional treatment on seizure outcomes remain to be described in the ARUBA randomized-controlled trial and Scottish population-based study.112,113

Two studies have directly compared conservative medical management with AEDs to interventional management for AVM-related epilepsy.114,115 Both were observational studies, one from the United States (which compared surgery to
Table 3 Rates per 100 person years (95% CI) or median proportion (95% CI) of complications following interventional therapy for AVMs118 for CCMs121

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<th>Surgery</th>
<th>Stereotactic radiosurgery</th>
<th>Embolization</th>
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<td>AVM</td>
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<td>Case fatality</td>
<td>1.1 (0.87–1.3)</td>
<td>0.5 (0.43–0.58)</td>
<td>0.96 (0.67–1.4)</td>
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<td>ICH</td>
<td>0.18 (0.10–0.30)</td>
<td>1.7 (1.5–1.8)</td>
<td>1.7 (1.3–2.3)</td>
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<td>Persistent focal neurologic deficita</td>
<td>7.4% (0.0–40%)</td>
<td>5.1% (0.0–21%)</td>
<td>6.6% (0.0–18%)</td>
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<td>CCM</td>
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<tr>
<td>Case fatalityb</td>
<td>0.3 (0.02–0.4)</td>
<td>0.3 (0.2–0.6)</td>
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<tr>
<td>ICHc</td>
<td>1.1 (0.8–1.4)</td>
<td>3.2 (2.7–3.9)</td>
<td>Not applicable</td>
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<tr>
<td>Persistent focal neurological deficit</td>
<td>4.3 (3.7–4.9)</td>
<td>1.2 (0.8–1.7)</td>
<td>Not applicable</td>
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Abbreviations: AVMs, arteriovenous malformations; CCMs, cerebral cavernous malformations; CI, confidence interval; ICH, intracerebral hemorrhage.
aReported as median proportion (95% CI).
bCase fatality directly attributable to CCM or treatment.
cSymptomatic ICH only.

Intracranial Vascular Malformations and Epilepsy

One of the United Kingdom (which compared any type of interventional treatment for AVMs to medical management). These two studies had similar sample sizes, population demographics, and AVM characteristics. Similar rates of AVM obliteration were obtained in the intervention cohort in each study (75%115 vs. 72%).114 During follow-up periods that ranged from 4.6 years to 13 years, neither study found a significant difference in the chance of achieving seizure freedom (risk ratio [RR] 1.11, 95% CI 0.69–1.80114, and RR 0.84, 95% CI 0.47–1.49).115

Many hospital-based case series have reported outcomes of AVM treatment for epilepsy management, but very few have been population-based or included control groups of patients whose AVMs were not treated. A recent systematic review and meta-analysis has attempted to quantify rates of seizure freedom according to each interventional modality. A total of 73% (mean follow-up of 4.5 ± 1.9 years) were seizure-free (duration unclear) following microsurgery, 62.9% (mean follow-up 3.6 ± 1.5 years) following stereotactic radiosurgery, and 50% (mean follow-up 3.8 ± 2.3 years) following embolization,116 but these data were extremely susceptible to selection and reporting biases, so these outcomes may well be overestimates. Complete AVM obliteration appeared to be associated with better chances of seizure freedom following stereotactic radiosurgery, but there were insufficient data available to study this in patients undergoing microsurgery or embolization.116 Few studies have addressed the role of multimodality interventional approaches to AVM-related epilepsy. Retrospective, single center experiences suggest that up to 70% can become seizure free using multimodality AVM therapy,41,117 although these estimates are again highly susceptible to selection and reporting biases.

The estimated benefits of intervention must be weighed against the putative risks. In those with no preintervention history of seizures, the proportion of patients with new onset postintervention seizures was 9.9% (54/547 patients) following microsurgery, 5.1% (29/568 patients) following stereotactic radiosurgery, and 33% (4/12 patients) following embolization according to one systematic review.116 Furthermore, a systematic review of 142 cohorts (comprising 13,698 patients with a 46,314 patient-years follow-up) indicated appreciable risks of case fatality, ICH, and permanent neurologic deficits following all three forms of invasive therapy.118

Therefore, available knowledge leaves us uncertain about the benefits of AVM surgery for seizure prevention and control overall, and a subgroup who benefit the most remains to be identified.

Cerebral Cavernous Malformations

The 5-year risk of a first-ever and recurrent intracerebral hemorrhage from a CCM is estimated at 2.4% (95% CI 0.0–5.7%) and 29.5% (4.1–55%), respectively.10 Functional deficits are mild following CCM-related ICH and do not appear to accumulate with recurrent hemorrhage.10 Interventional therapy (surgery or stereotactic radiosurgery) does not appear to have a dramatic effect (a RR > 10 or a p value < 0.01) on the risk of ICH recurrence in nonrandomized studies,119 and surgical excision of CCMs has been associated with worse functional outcomes that are sustained over at least 2 years during 5 years of follow-up.120 Furthermore, a recent systematic review and meta-analysis of 63 cohorts reporting on 3,424 patients found not inconsiderable risks of death, hemorrhage, and permanent neurologic deficits following surgical excision or stereotactic radiosurgery for CCM (~Table 3).121 There are insufficient comparative studies,119 and no randomized trials, on which to establish the optimal treatment approach. Hence, the same therapeutic uncertainties about AVM management also apply to CCMs.

A systematic review found that the literature on CCM treatment for intractable epilepsy is plagued by inconsistent definitions, poor descriptions of preoperative evaluation, limited details of the surgical technique, and a lack of standardized outcome measures.106 Given the nonrandomized, uncontrolled design of most of these studies, the best interventional approach remains uncertain, with some groups advocating a pure lesionectomy for selected cases,122–125 whereas others favor a standard extended lesionectomy.
Conclusions and Future Directions

We know that IVMs are important causes of seizures and epilepsy, and their identification following a first seizure has implications for AED treatment. But many uncertainties remain. Larger studies of the many potential predictors of seizure risk are needed, as are studies of associations with better treatment outcomes, but the greatest need is for randomized controlled trials.

Single-center studies of uncommon conditions, such as AVMs and CCMs, often lack the power to detect small but clinically meaningful results, leading to a proliferation of type II errors (false-negative results). Meta-analyses can be used to identify small but meaningful effects that may have otherwise gone undetected, but these have been challenging because of inconsistent definitions of clinical presentation and reporting of outcomes. Future prospective, multicenter studies should therefore aim to include unselected population-based cohorts; enroll patients at consistent time points within the disease natural history; use clearly defined terminology for clinical presentation, including consensus definitions of epilepsy and drug-resistant epilepsy; robustly characterize the untreated natural history of these conditions using consistent, objective measures of seizure freedom; and be of sufficient power to provide reliable estimates of prognostic variables. Recommended duration should be ≥ 1 year and completeness of follow-up should be ≥ 90%. In the absence of these studies, individual patient data meta-analysis may permit use of existing data. It is the optimal meta-analytic technique because it involves central processing of individual patient data from both published and unpublished datasets, uses consistent analytical approaches across cohorts, avoids the limitations of metaregression, and permits investigations of subgroups of interest.

Finally, we need randomized controlled trials of AVM and CCM treatment for the prevention of seizures. Higher-quality observational studies have failed to identify a dramatic treatment effect between conservative and medical management, and between different interventional techniques for CCMs in particular. Randomized trials could resolve the issue of whether conservative medical management is superior to interventional therapy in cases where there is doubt, and whether early surgery is preferable to delayed surgery. For those with drug-resistant epilepsy, a randomized-controlled trial conducted using epilepsy surgical rather than vascular surgical techniques would help to resolve the controversy regarding the optimal resection margins for CCMs and may help guide standard multimodality AVM treatment.

In the absence of high-quality data from RCTs, a standard epilepsy presurgical evaluation involving scalp video-EEG monitoring, and where necessary, invasive EEG recordings, PET, SPECT, and magnetoencephalography, is likely to be equally effective for IVM-related drug-resistant epilepsy as it is for people with other forms of epilepsy.

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