# Surgical treatment in super refractory status epilepticus related to arteriovenous malformation.

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***ABSTRACT***

***Introduction:*** *Brain Arteriovenous Malformations (AVM) are an abnormal set of dilated arteries and veins within the brain and are characterized by loss of vascular organization with an abnormal arteriovenous shunt. The probability of AVM rupture is low, but it can cause deficits in up to 45% of patients. Epilepsy could be associated with AVM, and status epilepticus is rare. The evolution to refractory status epilepticus or super refractory status epilepticus (SRSE) is very rare. The objective is to present a patient with epilepsy associated with non-ruptured AVM, treated with embolization and a subsequent complication that evolves into SRSE, in which a favorable resolution was achieved after surgery.* ***Clinical case:*** *70-year-old male, with a diagnosis of non-ruptured right temporal AVM and epilepsy, who has been seizure free since the diagnosis, is reported. Embolization of the AVM was performed, achieving total exclusion, after the procedure presented seizures that evolved into SRSE. After investigation, an AVM resection and partial resection of the ictal onset zone on the right parieto-temporal region was performed, including a disconnection of the central fronto-parietal region, where there was evidence of propagation of ictal activity. Patient recovered from the critical condition after surgery, and also presented electrographic normalization. After 2 years, the epilepsy is well controlled (Engel IIa).* ***Discussion and conclusions:*** *The surgical approach is an option in SRSE, and it should be proposed early on, within a reasonable time of evolution (1-2 weeks). The active approach in this case, where the surgery was done for SRSE control, was a successful intervention. Especially when the features are consistent -there is etiological evidence in imaging and electrical focality in studies- there can be a dramatic change in the prognosis.*

***Key words:*** *super refractory status epilepticus, brain arteriovenous malformation, epilepsy surgery.*

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## INTRODUCTION

Cerebral Arteriovenous Malformations (AVM) are abnormal set of arteries and veins dilated at a focal level within the brain parenchyma and are characterized by the loss of the normal vascular organization at the subarteriolar level, with a lack of a capillary bed that results in an abnormal arteriovenous shunt[1]. Its exact incidence is uncertain, and it is estimated to range between 1.0 and 1.3 per 100,000 inhabitants in a study in a Caucasian population[2] and 1.34 per 100,000 inhabitants in the prospective study "New York Islands AVM Study"[3]. Another report based on autopsies revealed that only 12% of patients with cerebral AVM were symptomatic[4]. The symptoms of cerebral AVM debut are varied[2], from the less frequent ones such as neurological deficit and headache, to the more frequent ones related to spontaneous intracerebral hemorrhages (30-50%) and seizures (20%).

AVMs are rare cerebrovascular lesions that are usually diagnosed during early adulthood and [its] expression with intracerebral hemorrhage can cause significant morbidity and mortality[5]. The incidence of spontaneous hemorrhage in AVM is approximately 0.5 per 100,000 people per year, with intraparenchymal hemorrhage being the most common, and less frequently subarachnoid or intraventricular[3,6]. It should be noted that approximately 10 to 20% of AVMs are diagnosed incidentally[6]. The risk of rupture of an AVM is estimated between 1 - 3%, if it is not treated. This risk increases from 2 to 5 times if there is a previous rupture, this being the most important predictive factor[7]. Other variables that increase the risk of rupture are advanced age, deep location and/or the presence of exclusive deep venous drainage[8]. Although the probability of AVM rupture is not a very high figure, mortality after this rupture ranges from 12 to 67%, likewise, it can cause severe deficits in patients up to 45%[9,10]. For this reason, current treatments focus mainly on the prevention of intracerebral hemorrhage[5], where it is recommended that AVMs be completely excluded. These treatments also turn out to be useful for the management of secondary epilepsy or to stabilize progressive neurological deficits.[8,11]

The epileptic seizures that occur in patients with AVMs usually have a focal onset and are usually controlled with the use of antiseizure medications (ASMs)[5]. The operational definition of Status Epilepticus (SE) distinguishes different types of SE considering both the semiology and the time duration; if it is convulsive, the temporal dimension of the operative definition is 5 min, but if it is focal with impaired awareness, it is 10 min, that is, they are not self-limited. On the other hand, Refractory Status Epilepticus (RSE) is defined when ongoing ictal epileptic activity is not controlled by first and second line ASMs[12]. If this situation is not reversed, it can evolve into Super Refractory Status Epilepticus (SRSE), defined as SE that continues for more than 24 hours despite treatment with anesthetics, including those cases in which seizures recur when reducing or trying to withdraw anesthetics[13]. It has been described that 12-43% of patients with SE progress to RSE and up to 10-15% may progress to SRSE[14]. The mechanisms by which SE evolves into a SRSE are not fully understood, but it has been proposed that after the onset of SE there is a progressive decrease in functionally active GABA receptors, as a result of their internalization, as well as a progressive increase in expression of active NMDA receptors in the postsynaptic membrane, with the increase of the Glutamatergic tone, contributing to the propagation and persistence of the epileptic activity[15]. The objective of this report is to present a patient with epilepsy associated with AVM, with embolization and subsequent complication that evolves into Super Refractory Status Epilepticus (SRSE), which was resolved with a resective epilepsy surgery approach.

## CLINICAL CASE DESCRIPTION

A 70-year-old-right-handed male patient, with a history of hypertension and dyslipidemia who had been under treatment. In 06/2016, he debuted with three generalized tonic-clonic seizures (GTCS). A brain computed tomography (CT) scan was

performed, revealing an image compatible with AVM, and focal epilepsy treatment was started with levetiracetam (LEV). In a subsequent study with magnetic resonance imaging (MRI), a non-ruptured right temporal AVM was revealed **(fig 1.a-b)**. Due to recurrence of seizures during 2018, valproic acid (VPA) was added on and an angiography was finally performed (06/2018), which showed an unruptured right temporal AVM (45 mm in diameter) with Spetzler Martin 3 flow aneurysm (fig 1.c-d). He was seizure free until 2019. It was decided to perform an embolization (01/2019), obtaining exclusion of 50% of the AVM. A second embolization was performed (05/2019), which achieved a complete exclusion **(fig 1.g-h)**. The patient presented recurrence of focal motor seizures in 06/2019, characterized by left faciobrachial clonic movements without impaired awareness. These seizures recurred in 08/2019, without achieving control with increasing doses of oral ASMs, rapidly evolving into a clinical pattern resembling an Epilepsia Partialis Continua, for which he was admitted to the Neurosurgery Institute Dr. Asenjo (INCA) in the Intensive Care Unit (ICU) (08/09/2019). He presented gradual consciousness deterioration, including bradypsychia and decrease in Glasgow Coma Scale (GCS) score. It later evolved into an RSE, as it did not respond to ASMs. Intubation and ASM polytherapy were required, and further ASM trials were attempted that included VPA, LEV, Clonazepam(CLP),Lacosamide(LCS),Topiramate (TPM), Phenytoin (PHT), Phenobarbital (PB) and Methylprednisolone (MTP). Treatment with infusion of benzodiazepines (Midazolam) and anesthetics (Propofol, Ketamine) was started as well, achieving a burst-suppresion pattern in the EEG. However, seizures reappeared when trying to suspend it 24 hours later, therefore a SRSE was diagnosed. A control MRI was performed showing an extensive and partially embolized right temporal AVM, with areas of right temporal cortical and right parieto-occipital necrosis, with thick surface drainage veins. Signal alteration was also observed in the right frontoparietal region that could correspond to vasogenic edema (flow dynamics), which pointed to an aggravating factor associated with epileptogenesis **(fig 1.e-f, i-j)**. A continuous EEG was performed during his stay in the ICU, with a first report done at admission and prior to anesthetic infusion that showed a disorganization of the background activity and the presence of lateralized periodic discharges at 1Hz over the right posterior temporal and centro-parieto-occipital head regions, at times also involving contralateral homologous head regions.

This pattern of Lateralized Periodic Discharges (LPDs) persisted, and was associated with ongoing altered mental status despite ASMs adjustments, in keeping with the diagnosis of RSE **(fig 2.a)**. Burst-suppresion pattern was achieved with anesthetic induction that was maintained for at least 6 days.

The Epilepsy Surgery team was consulted about the evolution of the SRSE, as the SE reappeared when trying to reduce the anesthetics and infusion of BZP. A prolonged 25-hour video electroencephalogram (VEEG) was performed (08/22/2019) **(fig 2.b-c-d)**, which showed a background activity in the theta frequency range at 4-6Hz with a low to medium voltage, symmetrically distributed over both hemispheres. No antero-posterior gradient or reactivity to stimuli was seen. This EEG showed also a frequent interictal epileptiform activity over right temporo-occipital head region, with a maximum negativity over occipital lead (O2), and several electrographic and electro-clinical seizures were captured during the recording (6 to 9 seizures per hour). Electrographically, the ictal EEG onset was characterized by periodic discharges at 0.5-1.0Hz over the right temporo-occipital region, evolving 5 to 8 seconds later into a beta-alpha rhythmic activity over the same region, and later into a rhythmic theta activity involving the same leads. Considering both the high frequency of seizures per hour of VEEG recording, and their average duration, they were considered compatible with a diagnosis of focal electrographic SE, also meeting the current criteria established by the ACNS (2021), which considers its diagnosis when electrographic seizures compromise 20% or more of a period of 60 minutes of recording[16]. The case was presented at a multidisciplinary epilepsy

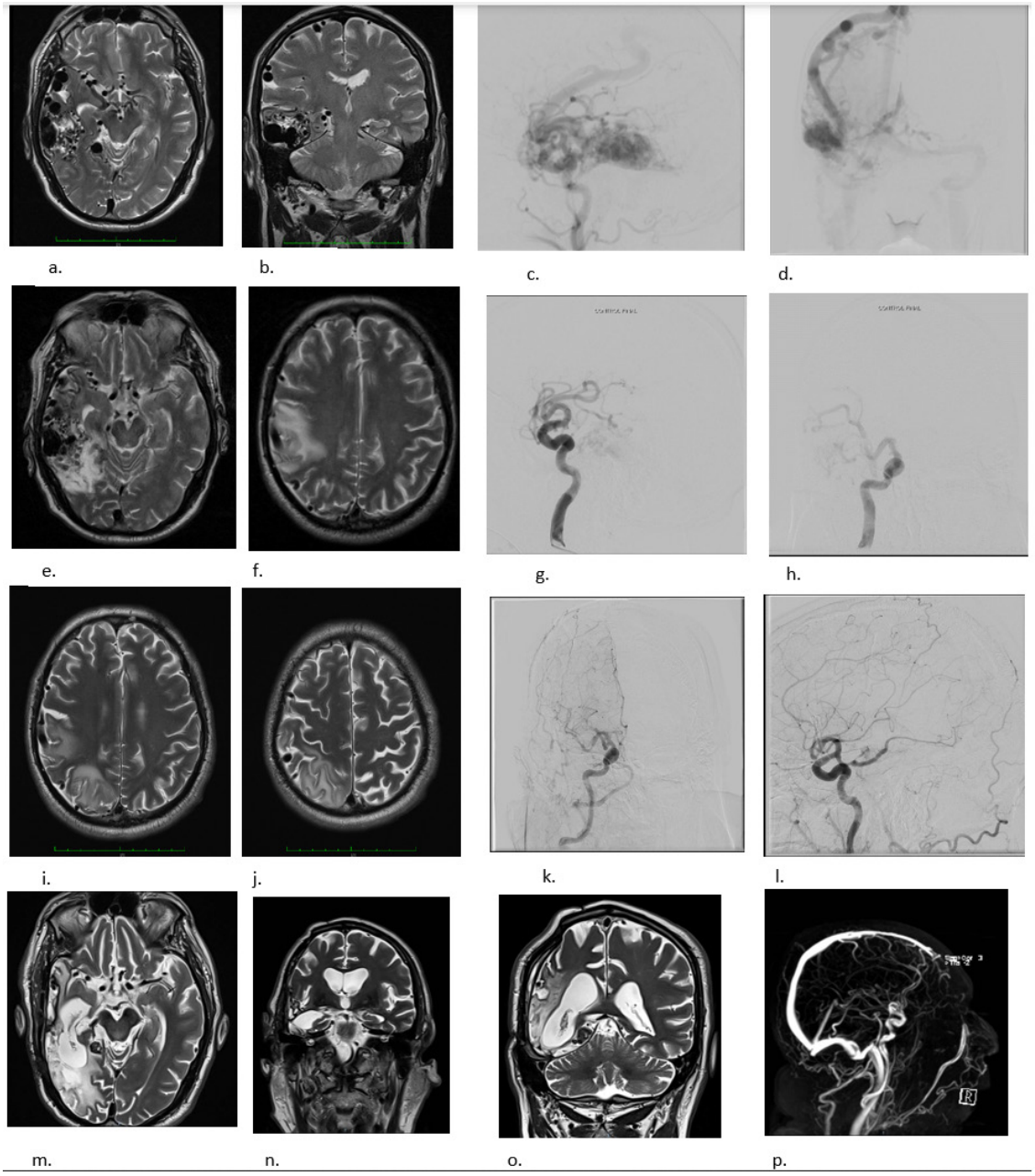


**Fig 1. (a-b)** MRI (2018) T2-weighted axial and coronal views: non-ruptured right temporal AVM; **(c-d)** Diagnostic angiography (2018) showing an unruptured right temporal AVM (45mm in diameter) with afferents from the temporal branches of the PCA and right MCA; outflow aneurysm in the right temporal branch of the PCA, Spetzler Martin 3; and mixed superficial and deep venous drainage; **(e-f-i-j)**. MRI (2019), T2-weighted coronal view showing extensive partially embolized right temporal AVM, with areas of temporal cortical and right parieto-occipital necrosis, and thick surface drainage veins. T2 signal alteration in the right frontoparietal region that could correspond to vasogenic edema (flow dynamics); **(g-h)** Post embolization angiography (05/2019): Embolized AVM with total exclusion; **(k- l)** Postoperative angiography (08/30/2021): Complete exclusion of right temporo-occipital AVM after embolization and surgery; **(m-n-o)** T2-weighted, axial and coronal views of the surgical bed with temporal resection of the AVM and cortical disconnection of the central sulcus (p) Last MR angiography reveals a complete exclusion of AVM.

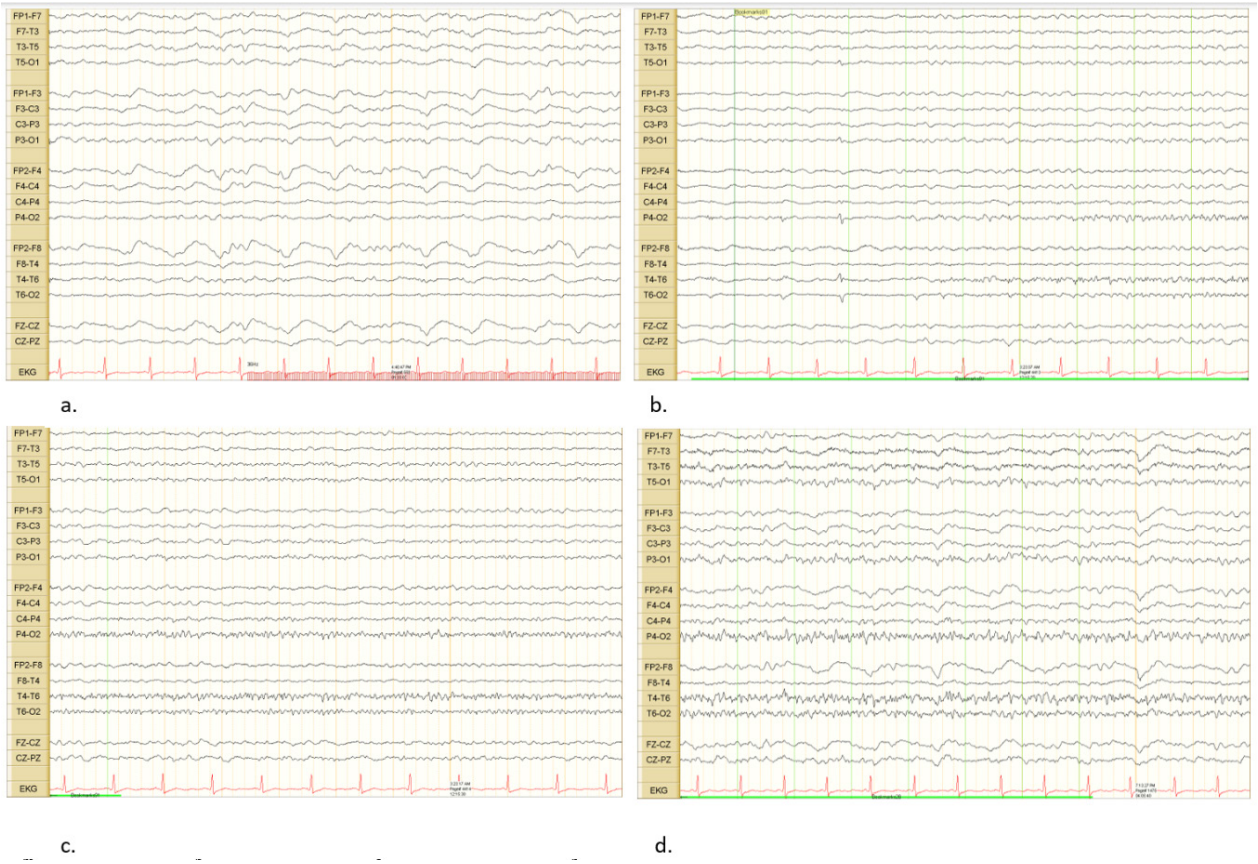


**Fig 2. (a)** EEG (08/12/2019): Background activity without an anterior to posterior gradient organization, accompanied by bilateral independent periodic discharges with slow wave morphology, showing fluctuation in frequency and maximum negativity over right anterior head region; **(b-c-d)** EEG (08/22/2019) Low-voltage background activity; during this recording, several right temporo-occipital focal onset seizures were captured, with a maximum negativity seen over T4-T6-O2 leads. They lasted between 90 and 180 seconds].

surgery meeting, and a surgical approach was proposed, which was discussed with the family, explaining scope, risks and possible benefits. Consent was obtained and the intervention was performed (08/27/19) with complete exeresis of the AVM, including the resection of temporal parenchyma in which extra and endovascular embolization material was observed. During the same procedure, subcortical disconnection of fronto-parietal U-fibers was performed, taking into account the anatomical and functional reference to the homunculus of the face and arm, using intraoperative neurophysiological monitoring; cortical motor stimulation helped to stablish safe limits for epileptogenic tissue resection, thus the motor cortex was spared.

As a result of this surgical intervention, the objective of stopping the SRSE was achieved, controlling the electro-clinical ictal activity. Within the first days of postoperative recovery, the patient achieved a GCS score of 14, with a mild left hemianopsia and mild left brachiocrural hemiparesis. Imaging studies such as angiography (08/2021) **(fig 1.k-l)**, MRI and MR angiography (07/2021) **(fig 1.m-n-o-p)** were obtained as control, showing a complete exclusion of the right temporo-occipital AVM. At the clinical follow-up at 2 years, the patient reported having sporadic right hemifacial focal motor seizures (Engel IIa). The patient achieved stability while standing and is now able to walk with aid, due to a mild left hemiparesis. No language deficits have been

reported. He maintains ongoing physiotherapy.

## DISCUSSION

Seizures represent the second most frequent symptom of presentation with cerebral AVM. One study described the clinical evolution of 2 groups of patients with epilepsy and AVM, assessing the probability of seizure freedom at 2 years: the first group was patients diagnosed with epilepsy before the diagnosis of cerebral AVM, which statistically associated a lower probability of seizure freedom; the second group of patients who had seizures as an initial symptom at the diagnosis of a cerebral AVM, presented a greater probability of seizure freedom at 2 years, this finding was also associated with a nidus smaller than 30 mm in diameter. In this patient as well as in the second group, seizures presented as an initial manifestation of AVM and a nidus diameter of 45 mm, both were associated with a favorable early evolution, achieving seizure freedom with only ASMs treatment for 1 year. Embolization and a possible secondary ischemic complication were time-related to epilepsy decompensation, which rapidly escalated to self-sustained seizures and an SRSE. In the second group, various seizure pathophysiological mechanisms have been proposed, such as those directly related to hemorrhage and hemosiderosis, as well as those secondary to vascular steal, perinidal edema, and factors related to the size and location of the nidus[11]. On the other hand, various therapeutic approaches have been proposed for cerebral AVMs, including close medical follow-up, particularly in cases without rupture, microsurgery, radiosurgery, embolization and, in the last case, the combination of the above. However, there is a lack of consensus on what the treatment of choice should be, where it has been proposed to consider, among other variables, age, clinical presentation, type of vascular nidus, size, location and vascular anatomy, which makes therapeutic decisions difficult.[6]

This case serves as a good starting point to discuss the association described between Epilepsy and AVMs, as well as the different therapeutic strategies proposed. In patients with epilepsy, the evolution towards SRSE is worrying, since mortality rates between 30 and 50% (13) and 13% of serious neurological sequelae[17] have been reported. To this date, there is no agreed protocol for its resolution. Treatment options are selected according to each particular clinical context. Facing the failure of pharmacological strategies and the prolongation of the SRSE, favorable evolutions have been reported with various surgical options, including focal, lobar or multilobar resections, hemispherectomies (anatomical, functional or modified), callosotomy and multiple subpial transections with or without focal resection[18]. On the other hand, the recommendation for treatment in AVM points towards a more active management in Spetzler grades 1-2, while in Spetzler grades 4-5 a more conservative treatment and clinical and imaging follow-up are suggested.[19,20]

Due to the lack of consensus on the treatment of unruptured Spetzler 3 AVMs, it has been proposed that this should be individualized patient by patient. This case shows how the embolization treatment generated a secondary complication in the form of a focal SRSE, which required to be evaluated with an epilepsy surgery strategy in mind, in order to address both the vascular lesion and the relevant epileptogenic network in a comprehensive manner. In this context, the decision of epilepsy surgery for this patient was made after a multidisciplinary team discussion that included both intensivists and the epilepsy surgery team, deciding on surgical treatment in view of the time of evolution of refractoriness of the SE. Multiple other variables were taken into consideration, such as the risk of associated morbidity and mortality of both the SE and the surgery, the use of various medical treatments and their therapeutic failure including the use of anesthetics, multiple ASMs and corticosteroids, among others, the presence of an extensive but focal lesion within the right hemisphere, and the lateralization and focalization of the epileptiform activity with the information obtained from the non-invasive neurophysiological study. Consent was obtained prior to the surgery, after an extensive conversation with the family in which it was clarified that the objective of the

surgical procedure consisted in trying to stop the SRSE although the patient could continue having seizures. Surgical risks were explained as well, emphasizing the complexity of combining vascular and epilepsy surgery techniques. Surgical planning had two objectives, to perform the AVM resection following vascular neurosurgery criteria, and to expand the resection to also include non-eloquent temporal parenchyma that was part of the epileptogenic zone defined by clinical, imaging and EEG findings. The disconnection of ictal propagation tracts connecting the epileptogenic zone to the precentral motor area of the face and arm was performed as well, trying not to injure the eloquent motor parenchyma. Once surgery was performed and the objectives of the proposed plan were achieved, subsequent rehabilitation treatment and maintenance of combined conventional ASM therapy favorably changed the prognosis that was originally proposed for this patient. It is important to emphasize that in these cases of SRSE that already have 2 weeks of evolution, the possibility of performing epilepsy surgery should always be considered. Thus, the collaboration, interaction and help between professionals from the epilepsy team and the ICU can determine a dramatic change in the prognosis of this condition. The mere fact of postponing decisions can have direct repercussions on the sequelae and risk of death in patients with SRSE[13]. The type of surgery and the optimal time to perform it is not clear in the literature. Focal resection has been recommended for patients with a well-defined ictal onset zone in non-eloquent cortex and persistent SRSE despite appropriate drug therapy (Level U, 7 class IV studies)[18]. Substantial morbidity and mortality are likely to accumulate the longer the duration of the SRSE. Some authors have suggested a period of two weeks of failed medical treatment as sufficient justification to consider surgery.[13]

## CONCLUSION

We presented a clinical case of a patient with epilepsy and AVM, that evolved into a SRSE after an ischemic/necrotic lesion secondary to an initially successful embolization that was later complicated by reperfusion and extravasation of embolization material. An intervention combining the vascular approach for the treatment of AVM and epilepsy surgery was performed, thus expanding the resection and disconnection of relevant epileptogenic tissues. By performing this combined approach, the surgery allowed the control of the SRSE and at the same time an adequate control of his epilepsy with Engel IIA at 2 years of follow-up. The need to approach epilepsy surgery in SRSE is highlighted, although the criteria and recommendations yet to be agreed upon in the literature.

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