



Review Article

Supratentorial cavernoma and epilepsy: Experience with 23 cases and literature review

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ABSTRACT

Background: The current study aimed to assess the role of microsurgical treatment of patients with supratentorial cavernoma with epilepsy based on analysis of our patients.

Methods: This retrospective study included 23 patients with supratentorial cavernoma on computed tomography (CT) scan and magnetic resonance imaging (MRI) of the brain admitted to the Department of Neurosurgery, Assiut University Hospitals (single tertiary hospital) between January 2014 and January 2018 (minimum 12-month follow-up). Deep-seated hemispheric and multiple cavernomas were excluded. Radiographs and hospital data of the patients were gathered and analyzed. All patients underwent the surgical procedure by one experienced neurosurgeon and the diagnosis was confirmed by pathologic evaluation.

Results: A total of 23 patients underwent surgical intervention consist of 15 (65%) men and 8 (35%) women. Their age varies from 11 to 59 year with an average of 36.6 years. All patients presented with seizure. The supratentorial cavernomas were located commonly in temporal lobes; 9 patients (39.1%). 19 (83%) of cavernoma located in the left side. 18 (78%) of cavernoma had a size <2 cavernoma. Complete excision was confirmed in postoperative investigations (CT and MRI brain images). All 10 patients with only one seizure preoperatively were seizure free at follow-up. Of nine patients who had experienced between two and five seizures preoperatively, 7 (78%) were seizure free, and of four patients with numerous seizures preoperatively, 3 (75%) were seizure free.

Conclusion: Our retrospective population study demonstrates an insight into the supratentorial cavernoma and suggests that microsurgical removal of the symptomatic cavernoma is generally accepted as the most effective and safe method.

Keywords: Cavernoma, Microsurgery, Seizures, Supratentorial

INTRODUCTION

Intracranial cavernous vascular malformations are variously known as cavernous angiomas, cavernous hemangiomas, or, more simply, cavernomas. Cavernomas are congenital low flow vascular lesions. It composed of irregular sinusoidal vascular channels, lacking smooth muscle, and elastic fibers. They lack feeding arteries or draining veins and contain no neural tissue.

The first description of an intracranial cavernoma was given by Virchow, in 1863. For over a century, it was considered to be an extremely rare malformation, usually found at autopsy, and exceptionally diagnosed during life. The prevalence of cerebral cavernous vascular malformations is estimated to be 0.4–0.9%.^[1]

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They can be found in several locations in the brain, but 70–80% of them are supratentorial. Supratentorial cavernoma most frequently present with new-onset seizures and progresses to medically refractory epilepsy in 40% of patients.^[15] Superficial cavernoma has a lower intracerebral hemorrhage (ICH) risk than the deeply located ones. More specifically, the ICH risk for infratentorial cavernoma is 3.8% but 0.4% for supratentorial cavernoma.

Cavernous malformations are dynamic lesions that may exhibit enlargement, regression, or even *de novo* formation.^[11,26] Although the mechanism of the growth of these lesions was not completely elucidated, most studies suggest that repeated subclinical bleeding episodes inside the lesion and the subsequent thrombus formation and trombolysis create the “caverne” that gives the name and the typical mulberry appearance on T2 magnetic resonance imaging (MRI).^[11] Because cavernomas can grow over time and bleed repetitively, follow-up imaging is important.

A true breakthrough in cavernoma diagnostics began with the widespread use of MRI. MRI allows cavernomas to be reliably diagnosed not only after acute neurological decline but also in asymptomatic incidental cases. Angiography is only able to detect the existence of abnormal venous drainage associated with cavernoma.

Surgical resection of symptomatic cavernoma lesions located in noneloquent areas is always recommended, as it has been shown to be safe as well as effective in treating epilepsy and preventing future hemorrhages.^[6,13] However, deciding on whether to resect a cavernoma becomes more complicated when the lesion is located in an eloquent area of the brain and is barely symptomatic or completely asymptomatic.

Complete removal of the lesion is required to prevent recurring hemorrhagic events but depends on the neurosurgeon’s experience.^[7] Resection of the hemosiderin ring must also be accomplished if seizure surgery is performed. Rebleeding has been shown to occur in 40% of cavernoma remnants after surgery, if remnants are found, surgical intervention is needed as early as possible.^[10]

This article reviews the basic surgical management of supratentorial cavernous malformations, reflecting the treatment strategies used at our department and analyze the factors that influence the outcome.

PATIENTS AND METHODS

General information

A total of 23 patients were included in this study underwent surgical excision from January 2014 to January 2018 in the Neurosurgery Department, Assiut University (single tertiary hospital). Diagnosis was assisted by computed tomography (CT) brain and MRI brain and confirmed by pathological

evaluation. Indications for cavernoma excision were made on inclusion criteria (supratentorial symptomatic cavernoma lesions located in easily accessible; safely removable and noneloquent areas with low morbidity associated with surgery). Deeply seated hemispheric and multiple cavernomas were excluded. Early surgery may be considered in situations with a high risk of bleeding, in patients unable to be compliant with antiepileptic drugs (AEDs) treatment, and in patients with a strong desire to eventually stop antiepileptic medication. Informed consent according to the criteria set by the local research ethics committee in our center had to be obtained in writing before surgery. The age of the patients ranged from 11 to 59 years with an average of 36.6 years [Table 1].

Clinical symptoms

All patients enrolled in this study were presented by seizures either focal in 17 patients or focal with secondary generalization in six patients.

Imaging examination

All cases were diagnosed based on CT scan and MRI on the brain. On CT, unless large, these lesions are difficult to see on CT. They do not enhance. If large, then a region of hyperdensity can be seen. If there has been a recent bleed, then it is more conspicuous and may be surrounded by a mantle of edema. In addition, all patients underwent MR

Table 1: Demographic data of patients in the studied period (2014–2018).

Variable	n (%)
Age	
20	3 (13)
20–40	11 (48)
40–60	9 (39)
Sex	
Male	15 (65)
Female	8 (35)
Type of seizure	
Focal	17 (74)
Focal with secondary generalization	6 (26)
Location	
Temporal	9 (39.10)
Frontal	7 (30.30)
Parietal	6 (26.10)
Occipital	1 (4.30)
Side of cavernoma	
Left	19 (83)
Right	4 (17)
Size of cavernoma (cm)	
<2	18 (78)
>2	5 (22)

scanning of brain and the entire spinal cord using the 1.5 T MRI system [Figure 1].

As could find on MRI, MRI is the modality of choice, demonstrating a characteristic “popcorn” or “berry” appearance with a rim of signal loss due to hemosiderin, which demonstrates prominent blooming on susceptibility weighted sequences. T1 and T2 signal are varied internally depending on the age of the blood products and small fluid-fluid levels may be evident. Size of the cavernoma can be estimated and divided into <2 cm (18 cases) and more than 2 cm (5 cases) with an average of 1.8 cm.

Surgical procedure

Removal of a cavernoma in patients with epilepsy should be assessed in the context of epilepsy surgery, implying indications for tailored surgery of the epileptogenic brain tissue. Failure to control epilepsy after an operation can be linked to incomplete resection and/or the persistence of a hemosiderin fringe.

The surgical procedure was chosen by the author neurosurgeon in a single center on the basis of comprehensive assessment of preoperative patients and intraoperative conditions. After careful analysis of MRI, we always carry out localizing procedures, to place the craniectomy exactly over the lesion. For that purpose, we sometimes use a frameless stereotactic device or neuronavigation system. We did not have motor, sensitive, or cranial nerves evoked potentials. Excision was done by craniotomy and was assisted by operative microscope [Figure 2].

Based on the information from the MRI, the surgical approach was directed on the shortest way to the lesion. We used a minimally invasive transsulcal approach to minimize cortical damage and to expose the lesion in a “keyhole” fashion. However, transcortical excision using intersulcal dissection may be used. The key method is careful dissection around the lesion, according to the principles of microsurgery. The microsurgical technique included sharp dissection and piecemeal resection or one-piece resection where possible in more superficial lesions. In the course of the dissection, afferent arterioles should be exposed, gently lifted up, and electrocoagulated one after the other. Neighboring veins should not be coagulated unless one is certain they drain the cavernoma exclusively. The lesion should be completely resected, including surrounding epileptogenic hemosiderin rich gliotic ring because subtotal removal of a cerebral cavernous malformation is associated with a high risk of recurrences.

The patients were followed up for at least 1 year. Clinical symptoms and signs were evaluated. Postoperative investigations (CT-MRI brain images) were asked routinely for the patients [Figure 3].

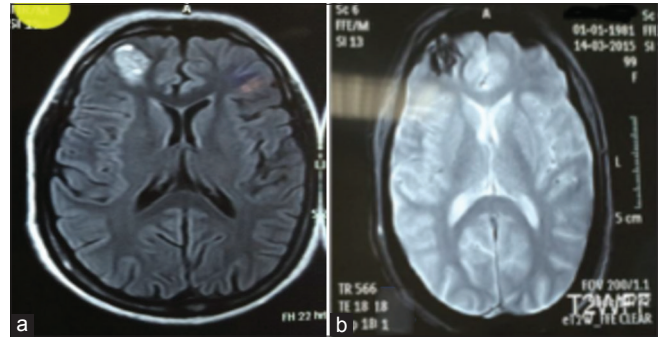


Figure 1: (a and b) Magnetic resonance imaging brain sagittal cuts T1- and T2-weighted images shows different characters of the cavernoma located in the right frontal lobe.

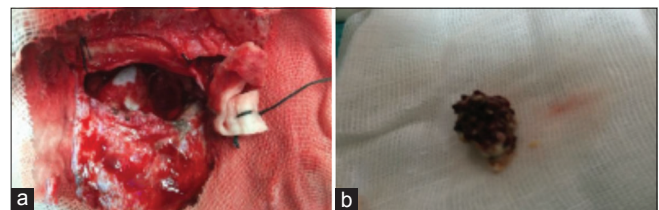


Figure 2: (a) After craniotomy and opening the dura and excision of the mass. (b) The mass after removal in one-piece fashion.

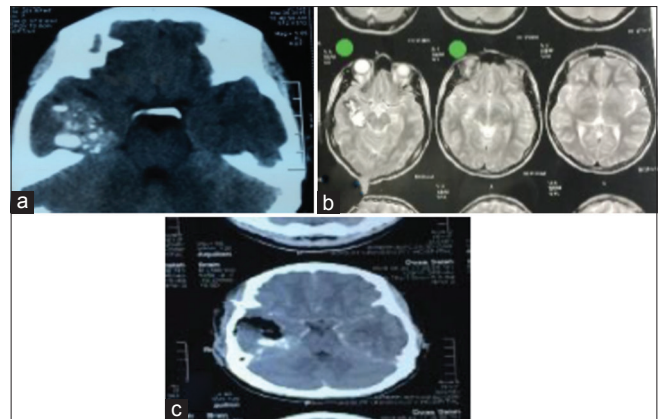


Figure 3: Male patient 35 years presented by focal seizures for more than 1 year in the left side. Computed tomography (a) and magnetic resonance imaging (b) showed the right temporal lesion. Excision was done and postoperative computed tomography (c) showed complete excision and histopathology revealed cavernoma.

Postoperative evaluation indexes

To evaluate the therapeutic outcomes, neurological and medical imaging examinations were performed. The general patient data and specific features before surgery and 12 months after surgery were recorded, respectively. Meanwhile, the clinical outcomes were evaluated using seizure manifestation. The symptoms were rated as “improved,” “unchanged,” and “deteriorated.” The postoperative anticonvulsants therapy is a continuation

of a preoperative one which was decided according to seizures types. The choice of the first AED for an individual with newly diagnosed seizures is of great importance and should be made taking into account high-quality evidence of how effective the drugs are at controlling seizures and whether they are associated with side effects. For examination in simple partial seizure, we prescribed a commonly carbamazepine, phenytoin, or valproic acid, and sometimes, we add adjunct therapy as topiramate or levetiracetam. In focal with secondary generalization subtype, we used mainly valproic acid and lamotrigine. The stoppage of antiepileptic medication was decided at follow-up visit; according to the patient clinical state, postoperative MRI brain, and postoperative electroencephalography (EEG) brain with sometimes video monitoring.

Statistical analysis

Data were collected in Excel sheet (Microsoft Office 2010), then were analyzed using SPSS version 22 (SPSS, Inc., Chicago, IL). The results were expressed in terms of frequency and percent.

Ethical consideration

The study was conducted after getting ethical clearance and the permission from Assiut University Teaching Hospital administration. Thorough explanation of the purpose of the study and how data will be treated with respect and confidentiality was provided to the participants. The study protocol was approved by the Ethical Committee, Faculty of Medicine, Assiut University, Egypt.

RESULTS

Demographic information

A total of 23 patients underwent surgical intervention consist of 15 (65%) men and 8 (35%) women. Their age varies from 11 to 59 years with an average of 36.6 years and the greatest number of the patients had 20–40 years old (48%).

Clinical results

Focal seizure was the common manifestation in 17 (74%) patients while focal with secondary generalization manifested in 6 (26%) patients. In this study, the clinical results 12 months after surgery were evaluated through reexamination visits. All 10 patients with only one seizure preoperatively were seizure free at follow-up. Of nine patients who had experienced between two and five seizures preoperatively, 7 (78%) were seizure free, and of four patients with numerous seizures preoperatively, 3 (75%) were seizure free.

Radiological results

The supratentorial cavernomas were located in temporal lobes in 9 patients (39.1%), frontal lobes in 7 patients (30.3%), parietal lobes in 6 patients (26.1%), and occipital lobes in 1 patient (4.3%). 19 (83%) of cavernoma located in the left side while 4 (17%) of cavernoma located in the right side. 18 (78%) of cavernoma had a size <2 cavernoma. Complete excision was confirmed in postoperative investigations (CT and MRI brain images).

DISCUSSION

Incidence

Cavernous malformations, also known as cavernous angiomas, cavernomas, or cryptic vascular malformations, are rare venous capillary bed abnormalities.^[34] Cavernomas comprise 5–13% of all cerebrovascular malformations.^[25] The sex distribution is equal; however, we have a male predominance in our series (15; 65% of patients).^[14]

Pathology and pathophysiology

The concept that cavernomas are static lesions has been revised due to growth seen on longitudinal neuroimaging studies and the presence of immunohistologic markers of angiogenesis and proliferation, such as vascular endothelial growth factor endoglin and proliferating cell nuclear antigen.^[33]

The pathophysiology of cavernoma-related epilepsy is likely to involve multiple mechanisms. Perhaps, more important are structural alterations observed in association with cavernomas: the hemosiderin deposit could, therefore, be an indicator that damage has occurred rather than being the main contributor to epileptogenesis. Indeed, a rim of astroglial reaction (astrogliosis) is a hallmark of cavernomas. Leakage of other blood constituents could also play a role; it is notable that albumin has been shown to be pro-epileptogenic through an effect on astrocytic function.^[29]

Astrocytes are well-known to play a role in epileptogenesis, possibly through their interaction with excitatory neurotransmitter release.^[28] An association between cavernomas and focal cortical dysplasia (FCD) was reported in literature^[22] and may be another potential pathomechanism of epileptogenesis. For adults who had a first cavernoma-related seizure, the 5-year risk of epilepsy is 94%.^[18] As with other etiologies, patients who have only focal seizures without secondary generalization may be more likely to become asymptomatic than those with secondarily generalized seizures.^[4]

Clinical symptoms

Most cavernoma (48%) are diagnosed incidentally on MRI scans performed for other reasons, but epileptic seizures

are the second most common initial clinical presentation, accounting for >25% of cases, and these patients usually have supratentorial cavernoma.^[6,24] Patients with cavernomas can present with any type of seizures. In our series, focal seizure was the common manifestation in 17 (74%) patients while focal with secondary generalization manifested in 6 (26%) patients. Several studies have investigated the correlation between epilepsy and cavernomas.^[23,31,32] Strong evidence supports cortical involvement as a main risk factor for epilepsy: 57–70% of “superficial” supratentorial lesions as compared to 14–20% of cavernomas with “deep” supratentorial localization were associated with epilepsy.^[1,20,24]

The onset of symptoms is usually in the third or fourth decade of life, as in our study, the greatest number of the patients had 20–40 years old (48%).^[19] Pediatric cavernomas are still diagnostically and therapeutically challenging lesions. Some studies show a better outcome in patients whose first seizure occurred after the age of 30 years.^[4,12] or 40 years,^[8] but others found no such effect.^[30,35]

Two studies found no difference in the occurrence of epilepsy as a function of lesion size,^[18,27] but others report a significant correlation between cavernoma diameter (including the hemosiderin rim) and the prevalence of epilepsy.^[23] In our study, 18 (78%) of cavernoma had a size <2 cavernoma. A diameter of <1.5 cavernoma associated with better seizure control during the first 2 years, but no differences arise at longer follow-up.^[4,35]

Radiology

There was an excess of temporal lobe lesions in the case series possibly resulting from a case selection bias toward intractable epilepsy. It has been suggested that temporal lobe cavernomas are more likely to be associated with intractability.^[9] In our series, the supratentorial cavernomas were located in temporal lobes in 9 patients (39.1%), frontal lobes in 7 patients (30.3%), parietal lobes in 6 patients (26.1%), and occipital lobes in 1 patient (4.3%). There seems to be no correlation between outcome and lobar location or side of cavernomas.^[4,8] We find the same result in our study.

The diagnosis of cavernomas is more difficult than other vascular diseases since cavernoma is angiographically occult malformations; thus, other imaging techniques are needed to provide an accurate diagnosis. Conventional T1- and T2-weighted MRI, gradient echo (GE) sequences, high-field MRI, susceptibility weighted imaging (SWI), diffusion tensor imaging, and functional MRI are some of the advanced techniques that are being used for diagnosis of cavernoma or for intraoperative navigation during the treatment of deeply located lesions.

The characteristic imaging appearance of a cavernoma is a multicystic lesion with cysts containing blood products of various ages and therefore various signal intensities

on T1- and T2-weighted imaging. A rim of hemosiderin should also be identified in GE or SWI sequences. There is no or only mild contrast enhancement and no surrounding edema unless there has been a recent associated parenchymal hemorrhage. Unless there is acute bleeding, cavernomas typically result in no mass effect since they replace rather than displace normal tissue.

Zabramsky^[36] developed a 4-grade classification of cavernous malformations based on MRI, in which Grade I is hyperintense, Grade II is both hyper- and hypo-intense, Grade III is hypointense, and Grade IV is small “black spot lesions” visible only on GE, these were considered capillary telangiectasias.

Management

In accordance with the current guidelines (Cavernoma Alliance UK, 2012; National Institute for Health and Care Excellence (NICE), 2012), they recommend that all cavernoma patients with a first seizure be urgently referred to a specialist with training and expertise in epilepsy (as neurologist author in our study) to assess whether the patient’s seizures are causally related to the cavernoma. The diagnostic workup should include anamnesis of epilepsy-specific history with analysis of ictal symptomatology as well as a wake and sleep EEG.

Many authors favor an initial conservative approach using AEDs in cavernoma patients with a single seizure rather than going to surgery directly.^[2,3,16] Early surgery may be considered in situations with a high risk of bleeding, in patients unable to be compliant with AED treatment, and in patients with a strong desire to eventually stop antiepileptic medication. Conversely, an initial conservative approach is favored in patients with cavernoma adjacent to eloquent brain regions and patients willing to carry the risk of bleeding. A prospective randomized study is necessary to resolve the question of immediate surgery versus medical treatment.

However, due to the risk of bleeding and the negative correlation between epilepsy duration and postoperative seizure outcome, the majority of authors feel that in patients with cavernoma it is not necessary to wait until the rigorous criteria of medically refractory epilepsy proposed by the International League Against Epilepsy are fulfilled.^[21] Failure of a single-drug trial with an adequate antiepileptic should be considered sufficient to recommend presurgical evaluation. More history of longstanding or frequent seizures, postoperative seizure outcome is less favorable as compared to patients with short seizure history or rare seizures.^[4] In our series, all 10 patients with only one seizure preoperatively were seizure free at follow-up. Of nine patients who had experienced between two and five seizures preoperatively, 7 (78%) were seizure free, and of four patients

with numerous seizures preoperatively, 3 (75%) were seizure free. Postoperative seizure outcome positive in patients in this series confirms the effectiveness of lesionectomy.

A longer preoperative history of epilepsy has been associated with worse seizure outcome. Most authors reported a significantly poorer outcome for patients with seizure duration over 1–2 years, with the notable exception of patients with sporadic seizures over a long period of time.^[17,35] A higher preoperative seizure frequency reportedly predicted worse postoperative outcome in some series. Considering that the cavernoma is often characterized by radiological changes and clinical progression, we felt that even one seizure warranted surgery in this particular group, thus reducing the likelihood of adverse events and decades of costly medications. Results of operative treatment of cavernoma reported previously and also documented in our patients confirm the effectiveness of this strategy.

Early microsurgical resection is an effective and safe therapy for patients with pharmacoresistant cavernoma-related epilepsy as well as for cavernomas with inherent risk of bleeding. Because cavernomas do not contain neuronal tissue, they cannot themselves be the ictal-onset zone or epileptogenic zone. Therefore, the surgical management of cavernoma is inevitably linked to their effects on the surrounding cerebral tissue. The lesion should be completely resected, including surrounding epileptogenic brain tissue because subtotal removal of a cavernoma is associated with a high risk of recurrences. Most studies report significantly better outcome when the surrounding gliosis and hemosiderin ring are removed.^[5,17,30,31] In our series, complete excision was done and confirmed in postoperative investigations (CT and MRI brain images).

Our study was limited by the nonrandomized group selection, the retrospective nature of the analysis, the low number of patients, and no comparative analysis with conservative management. The study subjects were ascertained along with many study variables using electronic medical records. These sources were not primarily designed for research purposes and could have had missing or incorrectly entered information. The strength of our study is that it was based on a defined population examined, operated, and followed up by a single investigator. Furthermore, it is a single center study; it may be helpful to enroll more medical centers, for better understanding of the nature course and management of supratentorial cavernomas.

CONCLUSION

In the present work, we summarized our results on the treatment of cavernomas; our findings are supported by literature. The most frequent manifestations of

supratentorial lesions are repeated seizures, which disturb the patient's life balance we identified a few risk factors for seizures such as the cortical and more frequently the temporomesial location, and the location in the left hemisphere. Microsurgery is the treatment of choice in symptomatic brain cavernomas, total resection being the only curative treatment, and capable to prevent further bleeding and to offer an efficient control of seizures. Complete cavernoma resection and resection of surrounding hemosiderin are recommended.

Declaration of patient consent

Research committee approval was obtained for this study from the institutions Medical Ethics Committee, Faculty of Medicine, Assiut University. Informed consent according to the criteria set by the local research ethics committee was obtained.

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Conflicts of interest

None of the authors has any conflicts of interest to disclose.

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