

CEREBRAL CAVERNOMAS IN THE ADULT. REVIEW OF THE LITERATURE AND ANALYSIS OF 61 SURGICALLY TREATED PATIENTS

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Background and Purpose. Authors review the latest data regarding modern, multimodal management of single and multiple intracranial cavernomas, based on their experience, on a consecutive series of 61 cases. **Methods.** During 2001 to 2009, 61 patients (33 men, 28 women) with intracerebral cavernous angiomas underwent surgical treatment in our center, and they were included into the present uncontrolled clinical study. The average age of the patients at the time of operation was 41.4 years. All patients underwent preoperative magnetic resonance imaging, and pre and postoperative clinical examination. The clinical course was documented using the Karnofski performance scale. A simplified version of Engel's classification of the outcome of the patients with chronic seizures was applied. **Results.** The most common clinical presentation of cavernous angiomas was seizures, significant part of which was chronic. In the group of patients presenting with headache, sporadic seizures, or intracerebral hemorrhage, good postoperative outcome was achieved in 86,84% of the patients. Of the patients who underwent operation for seizure control, significant seizure reduction or elimination after surgery was observed in 80,95% of the patients. **Conclusions.** Cavernomas are benign lesions, surgically resectable; the excision must be complete, any rests causing re-bleeding. Microsurgical removal of cavernous angiomas and surrounding hemosiderin plate tends to significant reduction or elimination of epileptic seizures and improved postoperative neurological status.

Keywords: cavernous angioma, cavernomas, epilepsy, hemorrhage, surgery

INTRODUCTION

Cavernous angiomas (CAs) or cavernomas are benign vascular malformations, which can be found at any region within the brain as well as in other organs (22, 33). CAs affecting the central nervous system represent approximately 5 to 10% of the central nervous system malformations (23, 24) and are present in about 0.4 to 0.8% of the population, according to the findings of autopsy series (26) and large magnetic resonance imaging (MRI)-based studies (13, 29). Most commonly, cavernomas are found at the supratentorial region (75%) and rarely in the brainstem, accounting for approximately 20% of all intracerebral cavernous angiomas (23, 24, 31).

Despite numerous case reports, retrospective or prospective studies and reviews, cerebral cavernous

angiomas remain as one of the most negotiable and controversial topics in neurological and neurosurgical practice. In the present study, we present a statistical evaluation of initial presentation, preoperative neurological findings, surgical and outcome of 61 consecutive surgically treated patients with intracerebral cavernous angiomas.

MATERIAL AND METHODS

Patients. During 2001 to 2009, 61 patients (33 men, 28 women) with intracerebral CAs underwent surgical treatment in Fourth Neurosurgical Department, Clinic Emergency Hospital "Bagdasar-Arseni", Bucharest, and these were included into the present uncontrolled clinical study. The average age of the patients at the

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time of operation was 41.4 years (age range, 18–72 years). All patients underwent preoperative MRI included standard T1- and T2- weighted sequences. A board-certified neuroradiologist reviewed all images. In each patient, lesions were identified based on typical characteristics and were classified according to number, location, size, and presence or absence of extralesional hemorrhage. Extralesional hemorrhage was defined as blood signal intensity extending beyond the low-signal-intensity rim of the lesion. The definition of hemorrhage was taken to be the presence of extralesional hemorrhage accompanied by a change in clinical status. 21 patients had a history of chronic seizures, and 11 patients presented with sporadic seizures. The data on age at the onset of seizures and the response to antiepileptic drugs were recorded retrospectively. All patients underwent pre- and postoperative clinical examination. The clinical course was documented using the Karnofski Performance Scale (KPS). A simplified version of Engel's classification of the outcome of the patients with chronic seizures was applied in the categories seizure-free, improved, no change, and worse (34).

Surgery. Operative removal of cavernous angioma was performed under standard microsurgical conditions. The surgical strategy was lesionectomy, limiting the removal to the CA and surrounding hemosiderin plate. In some patients, extralesional hematoma was also removed if it was present. Clinical follow-up data for the patients with chronic seizures were obtained at clinic visits.

RESULTS

There were 71 cavernous angiomas in 61 patients. Lesions were solitary in 55 patients (90,16%) and multiple in 6 patients (9,83%). Of the patients with multiple lesions, 3 had two lesions, 2 had three lesions and 1 had four lesions. The locations of 71 cavernous angiomas in 61 patients are presented in Table 1.

Table 1 Location of 71 cavernous angiomas in 61 patients

Supratentorial 59 (83.09%)	Subtentorial 12 (16.90%)
Frontal 24 (33.80%)	Cerebellar 5 (7.04%)
Temporal 21 (29.57%)	Brainstem 7 (9.85%)
Parietal 11 (15.49%)	
Occipital 2 (2.81%)	
Deep supratentorial (thalamus) 1 (1.40%)	

CT and MRI of cavernomas of different location are presented in Fig. 1-3.

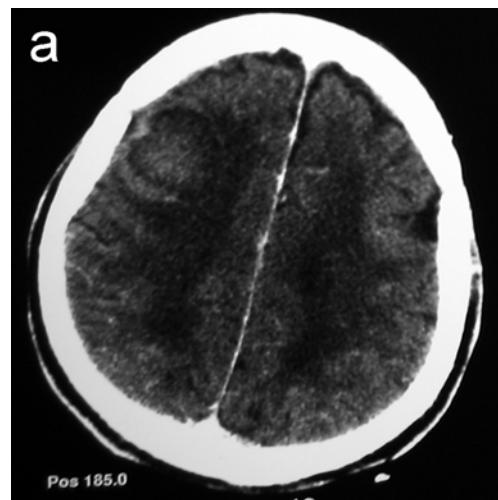


FIG. 1A

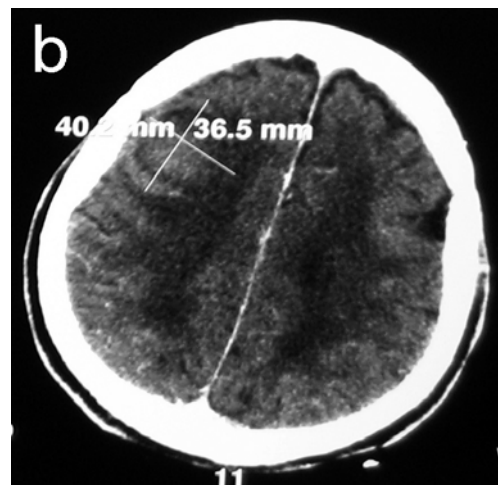


FIG. 1B

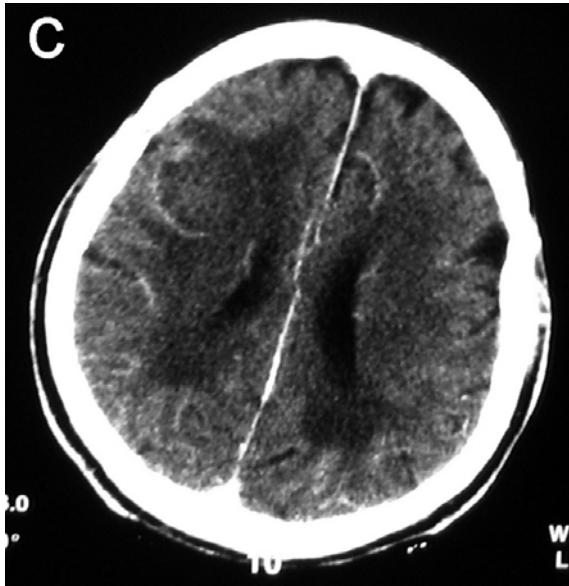


FIG. 1A,1B,1C CT cavernous angioma in the frontal lobe, sagittal section, native and contrast, revealing a isodense lesion with contrast ring enhancement, in a phase of subacute bleeding, with regional mass effect (male, 65 yo, frontal syndrome and sporadic seizures)

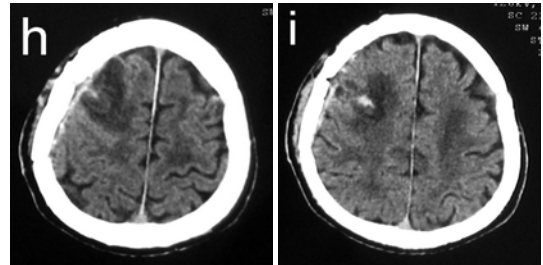


FIG. 1H,1I CT scan, axial sections, to the same patient, postoperative, without contrast, revealing a hipodense zone, in the area of the removed lesion

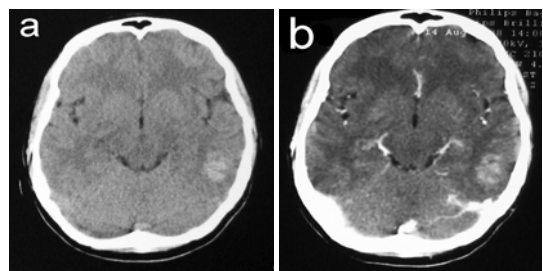


FIG. 2A, 2B Axial CT with contrast, of cavernous angioma, revealing pseudotumoral mass contrast enhancing, with perilesional edema, in the posterior temporal lobe, due to repeated bleeding and healing (female, 33 yo, chronic seizures)

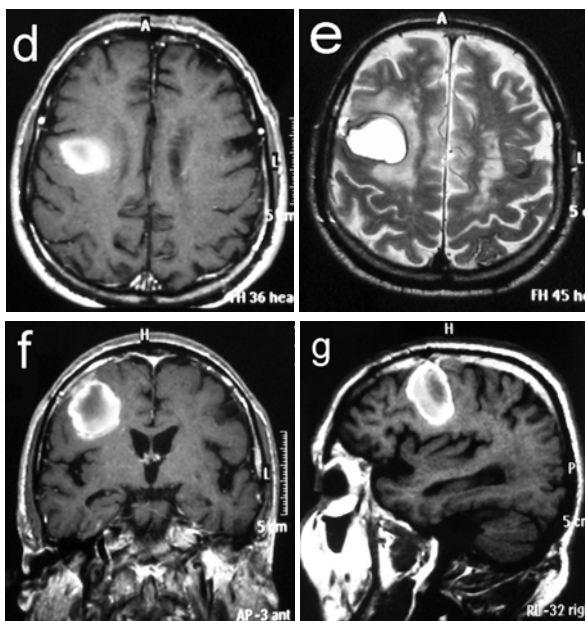


FIG. 1D,1E,1F,1G Preoperative MRI, axial, sagittal, and coronar sections, T1 and T2, to the same patient, revealing subacute bleeding with hemosiderin products, and regional mass effect

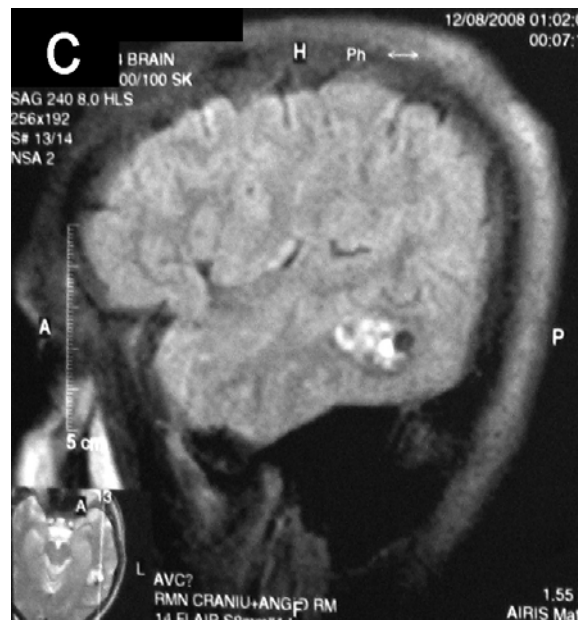


FIG. 2C

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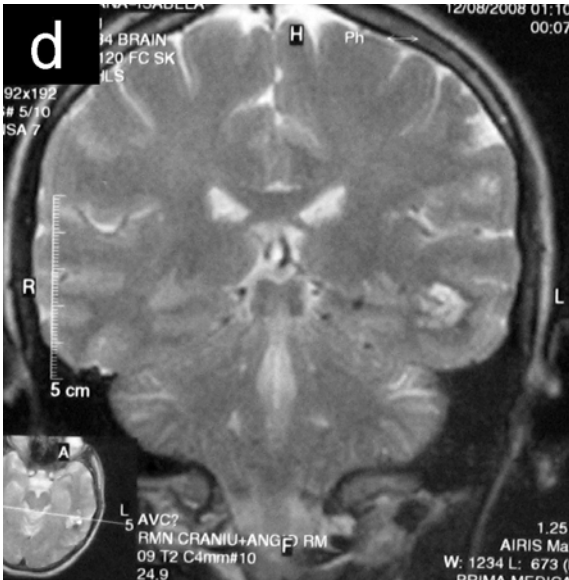


FIG. 2D

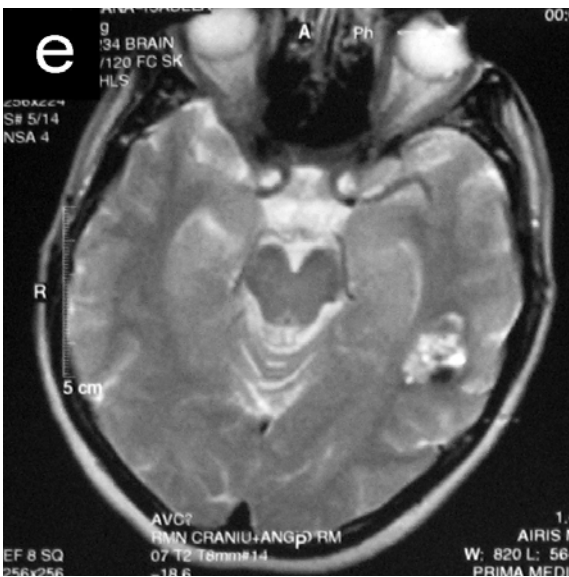


FIG. 2E

FIG. 2C, 2D, 2E Preoperative MRI, sagittal, coronar and axial sections, T2 with contrast, revealing gliotic peri-lesional area with different age hemosiderin products, in the same patient

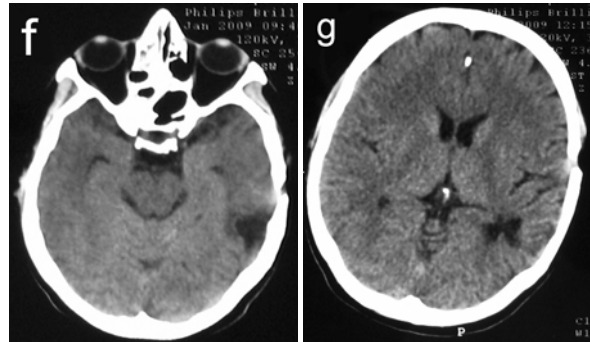


FIG. 2F, 2G Postoperative axial CT without contrast, revealing the hypodense area of the resected lesion

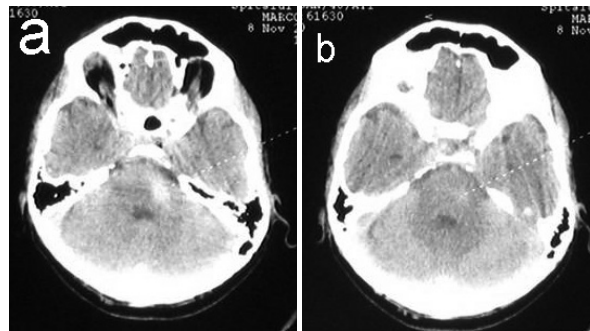


Fig. 3A, 3B CT scan of cavernous angioma in brain stem, revealed with trauma occasion in a patient of 37 yo, who suffered a car crash. In the image appears a small hematoma within the left cerebellar peduncle

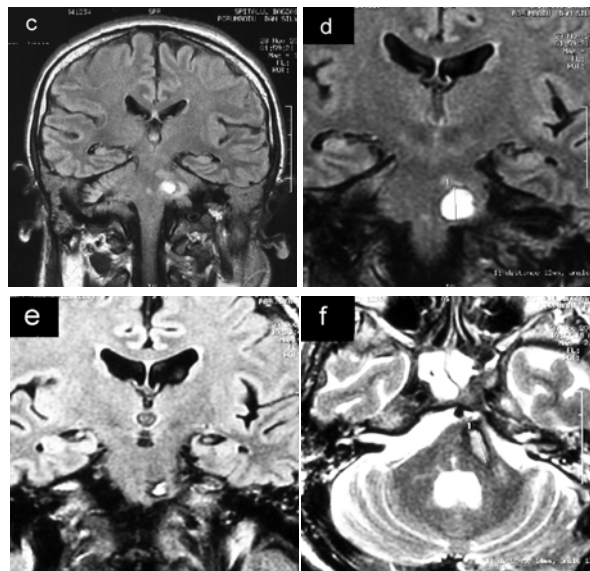


FIG. 3C, 3D, 3E, 3F

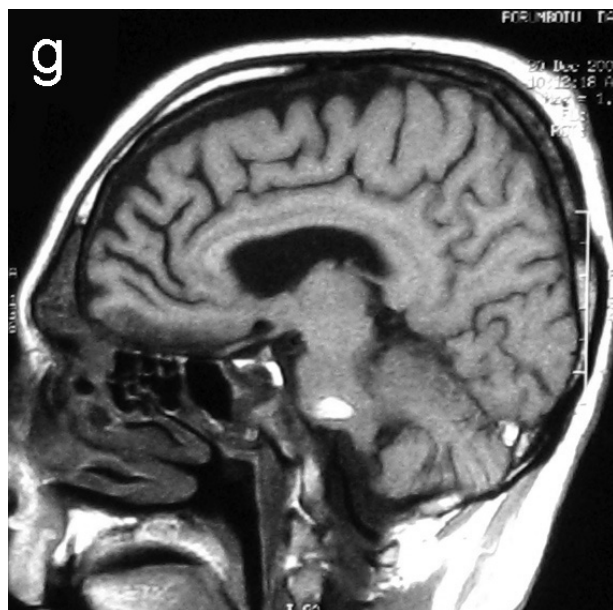


FIG. 3G

Fig. 3C, 3D, 3E, 3F, 3G Magnetic resonance imaging in the same patient, coronar sections T1, axial sections T2, and sagittal sections T1, without contrast, in the subacute phase, revealing the tumoral nodule and perilesional hemosiderin ring, corresponding to hematoma resorbption

At initial presentation, headache was reported in 19 patients, seizure in 32, and focal neurological deficit in 27 (Table 2). Twenty-one (34.42%) patients presented with symptomatic extralesional hemorrhage. There were no statistically significant differences between males and females in regard to initial clinical presentation.

Table 2 Clinical presentation of 61 patients with cavernous angioma*

Headache No(%)	Seizure No(%)	Focal deficit No(%)	Hemorrhage No(%)
19 (31.14)	32 (52.45)	27 (44.26)	21 (34.42)

*Some patients presented with more than one symptom.

The size of cavernomas ranged from 0.3 cm to 5.0 cm (median, 2.0 cm) in their largest diameter.

21 patients with seizures had a history of chronic epilepsy and a longer mean duration of illness; 11 patients had only single or sporadic seizures and a fast diagnosis of cavernous angioma and surgical treatment. Four patients with seizures had multiple lesions. This accounted for 66.66% (4/6) of all patients with multiple lesions in a group. The results of the preoperative neurological examination were normal in 23 patients.

The other 9 had focal neurological signs. Five patients had intracerebral bleeding, which in 3 of these 5 was subsequent to the onset of epilepsy. After exclusion of patients with multiple lesions, temporal location of cavernous angioma was more frequent in both the patients with chronic seizures and those with sporadic seizures. According to the KPS, out of 38 patients presenting with headache, sporadic seizures, or intracerebral hemorrhage, preoperative neurological status was inferior or equal to 70 in 12 patients and superior or equal to 80 in 26. In 33 (86.84%) patients of this group, the KPS score at discharge was 80 to 90 (good outcome).

Table 3 Clinical presentation by lesion location in 55 patients with single lesion

Lesion location	Patients No	Headache No(%)	Seizure No(%)	Focal deficit No(%)	Hemorrhage No(%)
Supratentorial	47	15(31.91)	28(59.57)	17(36.17)	16(34.04)
Frontal	19	4(21.05)	10(52.63)	8(42.10)	7(36.84)
Temporal	20	7(35)	14(70)	5(25)	6(30)
Parietal	7	4(57.14)	3(42.85)	4(57.14)	3(42.85)
Occipital	1	-	1	-	-
Subtentorial	8	3(37.5)	-	8(100)	3(37.5)
Cerebellar	3	2(25)	-	3(100)	1(12.5)
Brainstem	5	1(12.5)	-	5(100)	2(25)

Poor outcome was defined by death in 1 patient (2.63%) or a postoperative KPS inferior or equal to 70 in 4 patients (10.52%). Postoperative focal neurological signs (sensorimotor defects) were present in 3 patients (7.89%). Of the 21 patients who underwent operation for seizure control, 17 (80.95%) reported significant seizure reduction or elimination after surgery. Three patients reported the same frequency and type of seizures as before operation. Worsening of epileptic seizures was observed in one patient (4.76%) of the group.

DISCUSSION AND LITERATURE REVIEW

Cavernous angiomas are considered congenital vascular hamartomas composed of closely approximated endothelial-lined sinusoidal collections without significant amounts of interspersed neural tissue. Cavernous angiomas are not encapsulated, but well separable from brain parenchyma. However, the surrounding brain usually exhibits evidence of prior microhemorrhage, hemosiderin, discoloration, and hemosiderin-filled macrophages. This indicates recurrent microbleedings or leakage of red blood cells. Thrombi of varying age are characteristic and are present within many of the vessels. Calcification and surrounding gliosis typify the margins of the lesion.

Although CAs have been generally regarded as congenital lesions that arise as a result of disordered mesodermal differentiation during the early stages of embryogenesis, recent studies have documented the growth and "de novo" appearance of sporadic or familial CAs (15). Repeated intralesional microhemorrhages and their breakdown products can also initiate a series of responses such as cellular proliferation and fibrosis that promote new vessel formation and hemorrhagic angiogenic proliferation. However, the molecular mechanisms underlying the genesis and maintenance of these abnormal vascular phenotypes are not well known. Despite many detailed radiologic and pathologic studies on the subject, controversy still exists regarding their classification as true vascular malformations or as capillary vessels slow-growing tumors, due to their occurrence and

growing pattern, which is still incomplete elucidated (35).

Cavernomas may occur sporadically (18), after radiation therapy (3) and hereditarily following an autosomal dominant trait (19).

Cavernous angiomas can be found in any part of the brain because they can occur at any location along the vascular bed. Frontal and temporal lobes are the most common sites of occurrence (8), and 80-90% of the lesions are supratentorial (11, 13, 22). Cavernomas are preferentially located cortically or in the subcortical white matter. A deep location in the basal ganglia, hypothalamus, or ventricular system is infrequent. In our series, just one patient had a cavernous angioma located in the right thalamus.

Cerebral cavernomas are dynamic lesions that are prone to vary in number and size over time (2, 27). The size of cavernomas reported in the literature ranges from 0.1 cm to 9 cm in their largest diameter (21). Usually cavernomas reach a larger size in children (6.7 cm on average) than in adults, in whom it tends to be 2-3 cm (25). We have not observed such a tendency, as two largest cavernomas were observed in 24- and 32-year-old female patients. Well in accord with the results of other studies, we have also found no associations between size of cavernoma and the initial presentation of cavernoma (25, 30).

Many authors have reported imaging and/or surgical evidence of an association between cavernoma and local developmental venous anomalies (1, 20). In our series, just one patient had venous angioma in addition to cavernous angioma what is much lower compared to other reports.

Most studies support equal male/female prevalence for CAs (13,16, 29), and our results confirm these findings.

According to the literature, the prevalence of multiple cavernoma varies between 3% and 50% (22, 23, 24, 28). In our series, nearly 10% of the patients had multiple cavernomas.

Patients with cavernous angioma present with a variety of symptoms. Seizures are reported as the most common symptom, accounting for 38%-55% of patient's complaint.

Other symptoms include focal neurologic deficits in 12%–45% of patients, recurrent hemorrhage in 4%–32%, and chronic headaches in 5%–52% (11, 13, 22, 30). Intracranial hypertension syndrome and/or focal neurological deficits are usually related to acute hemorrhage, which is recognized as the first clinical presentation in nearly 40% of cases (13, 22, 33). Any hemorrhage found on CT scans in a relatively young patient should be characterized further, and cavernous angioma must be considered a possible etiology. In the workup of a patient with a seizure disorder, cavernous angioma must be considered the underlying etiology, especially if the patient is aged 20-40 years. Brainstem cavernomas nearly never cause seizures. Most of these patients do have typical brainstem symptoms like diplopia, face or body sensory disturbances, or ataxia. Without imaging, this subgroup of patients with infratentorially located cavernomas can closely mimic the clinical picture of multiple sclerosis. The majority of patients become symptomatic between the third and fifth decade, and there is no definite association between symptoms and gender. The frequency of asymptomatic cavernomas is not precisely known, but according to the reports of Zabramski et al. (36) and Brunereau et al. (4, 5) it seems to be as high as 40%.

Thus, our series is not different and fits well within the reported ranges. Most common clinical presentation of CAs was seizures (52,45%), significant part of which was chronic. 34.42% patients presented with symptomatic extralesional hemorrhage. No significant differences in the likelihood of presenting with hemorrhage between supratentorial and subtentorial lesions were detected. 31,14% patients presented with headache and 44,26% with focal deficit.

MRI is the method of choice for the long-term follow-up of patients with cavernous angiomas and for the assessment of family members in whom similar lesions are suspected. In addition, MRI is extremely helpful in presurgical planning to assess the extent of the lesion, define borders, and plan the surgical approach and exposure. Most cavernous malformations are angiographically occult, and when they are evident on angiograms, the findings are nonspecific. When the lesions occur in combination with other vascular malformations, as they do in as

many as 30% of patients with venous malformations, MRI characteristics become more complicated and less specific. In these patients, angiography can be helpful in further defining the lesions.

Treatment indication in cavernous angioma depends mainly on the natural course of the lesion, as well as its location and surgical accessibility. The latter depends on the skill of the surgeon and the position of the lesion relative to eloquent areas of the brain. In general, therapeutic strategies include: observation of patients with asymptomatic or inaccessible lesions; surgical excision of symptomatic and accessible lesions; radiosurgery for progressively symptomatic but surgically inaccessible lesions (questionable). The recommendations for the management of patients with cavernous angioma have varied throughout the years and are still not homogeneous.

Treatment of intracranial cavernomas must be individualized in each patient. A multidisciplinary medical team, formed by specialists in cerebrovascular pathology (neurologist, neurosurgeon, neuroradiologist), together with the patient and his family, decide whether treatment is mandatory and which is the best therapeutical option.

Difficulties and controversies in decision making are especially in asymptomatic, incidental or deep lesions, without hemorrhage.

In the group of patients presenting with headache, sporadic seizures, or intracerebral hemorrhage, good postoperative outcome was achieved in 86.84% of the patients. Of the patients who underwent operation for seizure control, significant seizure reduction or elimination after surgery was observed in 80.95% of the patients.

Our results indicate that the excision of CAs leads to a favorable epilepsy outcome as it was pointed out by other studies (14,22). A proportion of those seizure-free or with a marked reduction in seizure frequency was somewhat higher than that reported by Churchyard et al. (9) or by Moran et al. (22) yet lower compared to the overall positive effect of surgery in which up to 94% of the patients became seizure-free, or at least experienced a marked reduction in seizure frequency (6,11,32,33). The unfavorable epilepsy outcome

observed in one patient of our series was presumably caused by the presence of multiple CAs.

In order to cure epilepsy, according to some authors it is necessary to remove the hemosiderin capsule surrounding the malformation (11,12) and possibly representing an irritating element (17,33). Other authors do not judge this to be necessary because it is in many cases difficult to discern it from the surrounding compressed or atrophied brain (25) or because they failed to find any substantial evidence that the additional excision of the hemosiderin-stained tissue around the cavernoma provided better results than merely resection of the cavernoma (7,37). We prefer to remove the hemosiderin plate surrounding the cavernoma as we support the hypothesis that breakdown products of blood could facilitate the initiation of seizures (17,33).

CONCLUSION

Cavernomas are benign lesions, surgically resectable; the excision must be complete, any rests causing re-bleeding. Asymptomatic patients are encouraged to live a normal life, without any solicited physical activity. Removal of cavernous angiomas together with surrounding hemosiderin plate or/and intracerebral hemorrhage using microsurgical techniques was relatively safe procedure that significantly reduced the frequency or even eliminated epileptic seizures as well as improved postoperative neurological status in the majority of our patients with chronic seizures, and with headache, sporadic seizures or intracerebral hemorrhage, respectively.

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