

Cavernous angiomas: an uncontrolled clinical study of 87 surgically treated patients

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Key words: cavernous angioma; epilepsy; hemorrhage; surgery.

Summary. *Background.* Cerebral cavernous angiomas remain as one of the most negotiable and controversial topics in neurological and neurosurgical practice. We present statistical evaluation of initial presentation, preoperative neurological findings, surgical complications, and outcome of surgically treated patients with intracerebral cavernous angiomas.

Methods. During 1997 to 2004, 87 patients (41 men, 46 women) with intracerebral cavernous angiomas underwent surgical treatment in the tertiary referral center; and these were included into the present uncontrolled clinical study. The mean age of the patients at the time of operation was 42.4 years, and the mean duration of illness was 120.5 days. 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. No association was found between lesion location by cerebral lobes and clinical presentation by seizures. No significant differences in the likelihood of presenting with hemorrhage between supratentorial and subtentorial lesions were detected. In addition, no associations were found between size of cavernoma and the initial presentation of cavernoma by an extralesional hemorrhage or chronic seizures. In the group of patients presenting with headache, sporadic seizures, or intracerebral hemorrhage, good postoperative outcome was achieved in 83% of the patients. Of the patients who underwent operation for seizure control, significant seizure reduction or elimination after surgery was observed in 79% of the patients.

Conclusions. Microsurgical removal of cavernous angiomas and surrounding hemosiderin plate tends to significant reduction or elimination of epileptic seizures and improved postoperative neurological status.

Introduction

Cavernous angiomas (CAs) are benign vascular malformations, which can be found at any region within the brain as well as in other organs (1, 2). CAs affecting the central nervous system represent approximately 5 to 10% of the central nervous system malformations (3, 4) and are present in about 0.4 to 0.8% of the population, according to the findings of autopsy series (5) and large magnetic resonance imaging (MRI)-based studies (6, 7). Most commonly, cavernomas are found at the supratentorial region (75%) and rarely in the brainstem, accounting for approximately 20% of all intracerebral cavernous angiomas (3, 4, 8). The cavernous angioma is a recognized cause of partial epilepsy, especially in case of intractable

seizures. If cavernous angiomas bleed, they can cause severe functional disturbance or death.

Since the implementation of MRI into the clinical practice in Lithuania in 1997, preoperative diagnosis of CAs has become feasible. 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. To our knowledge, there were no studies on this topic reported from the Eastern European countries. Therefore, in the present study, we present a statistical evaluation of initial presentation, preoperative neurological findings, surgical complications, and outcome of 87 consecutive surgically treated patients with intracerebral cavernous angiomas.

Patients and methods

During 1997 to 2004, 87 patients (41 men, 46 women) with intracerebral CAs underwent surgical treatment in the tertiary referral center, Department of Neurosurgery of the Hospital of Kaunas University of Medicine, and these were included into the present uncontrolled clinical study. The mean age of the patients at the time of operation was 42.4 years (95% confidence interval (CI), 38.9–45.6 years) (age range, 10–72 years; median, 41 years), and the mean duration of illness was 120.5 ± 57.4 days.

All patients underwent preoperative MRI. MRI scans were performed on 1 Tesla machines and 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.

Thirty-three patients had a history of chronic seizures, and 17 patients presented with sporadic seizures. All these patients underwent scalp electroencephalography (EEG) with hyperventilation and photo stimulation by use of 16-channel bipolar recordings. 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 (9).

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. Clinical status was judged as such at the last visit but before May 20, 2005.

Statistical analysis was performed using χ^2 and Fisher's exact two-tailed test for comparison of proportions. To test a difference between the medians of

two independent groups, the nonparametric Mann-Whitney *U* test was used. Significant differences were considered at the $P < 0.05$ level.

The study was approved by the Kaunas Regional Bioethics Committee in 1997 (protocol No. 33/97). Written consent was obtained from all patients included into the study.

Results

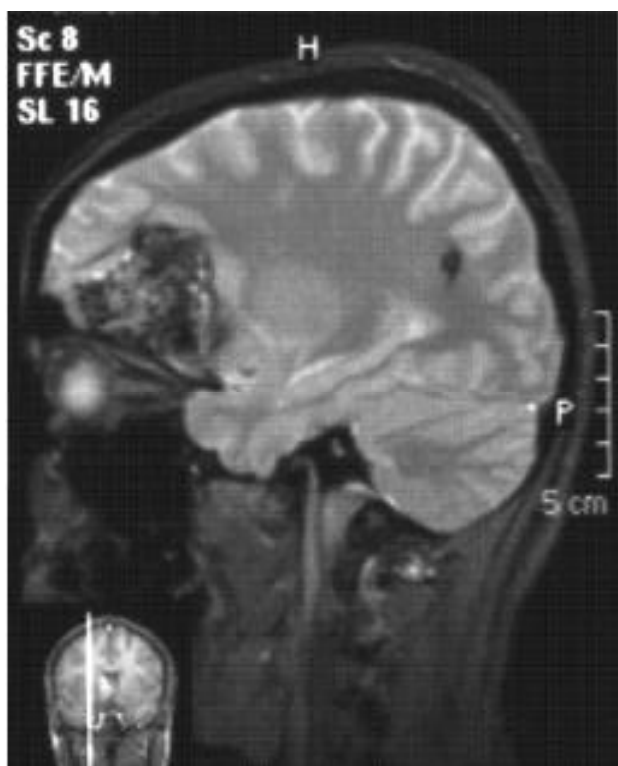
There were 108 cavernous angiomas in 87 patients. Lesions were solitary in 76 patients (87.4%) and multiple in 11 patients (12.6%). Of the patients with multiple lesions, 6 had two lesions, 3 had three lesions, 1 had four lesions, and 1 more than four lesions. Of the 11 patients with multiple CAs, 10 were female. The locations of 102 cavernous angiomas in 87 patients (only the one largest lesion in a patient with multiple lesions is included) are presented in Table 1. MRIs of cavernomas of different location are presented in Fig. 1–3. Coexisting cerebrovascular lesions were found in 4 patients: 3 arterial aneurysms and 1 arteriovenous malformation.

Table 1. Location of 102 cavernous angiomas in 87 patients

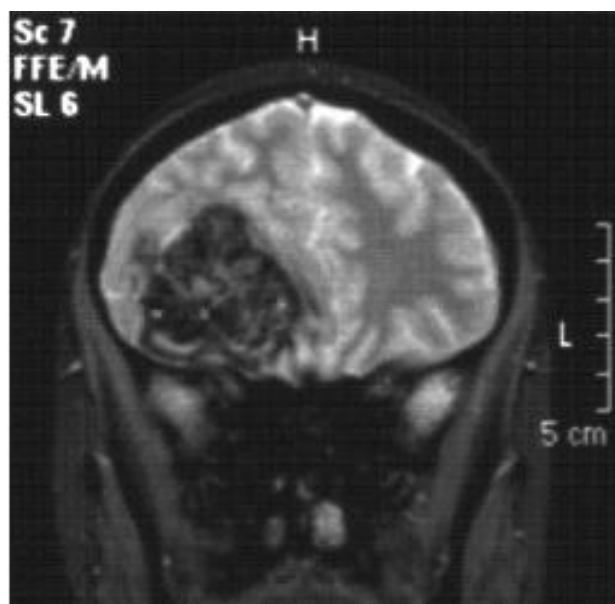
Location	N (%)
Supratentorial	85 (83.3)
Frontal	36 (35.3)
Temporal	33 (39.3)
Parietal	12 (11.8)
Occipital	3 (2.9)
Deep supratentorial (thalamus)	1 (1.0)
Subtentorial	17 (16.7)
Cerebellar	8 (7.8)
Brainstem	9 (8.8)

At initial presentation, headache was reported in 31 patients, seizure in 51, and focal neurological deficit in 40 (Table 2). Twenty-three (26.4%) patients presented with symptomatic extralesional hemorrhage. Nineteen (82.6%) patients with extralesional hemorrhage had a focal neurological deficit, compared with 19 (31.1%) of 61 patients without hemorrhage ($P = 0.0001$). There were no statistically significant differences between males and females in regard to initial clinical presentation except that for focal deficit, which was more common among females ($P = 0.01$).

Table 3 demonstrates clinical presentations by lesion locations in 76 patients with single lesions. The patients with supratentorial lesions were significantly more likely to present with seizures as compared to



A

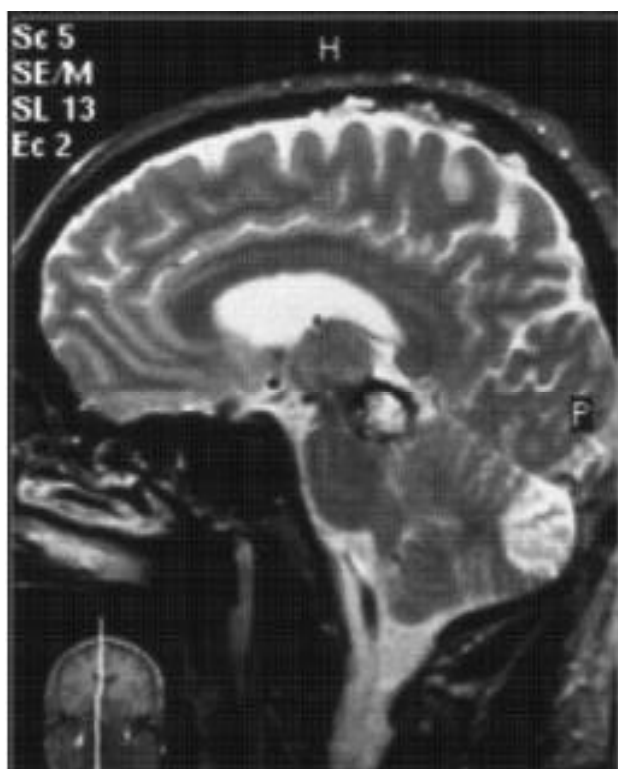


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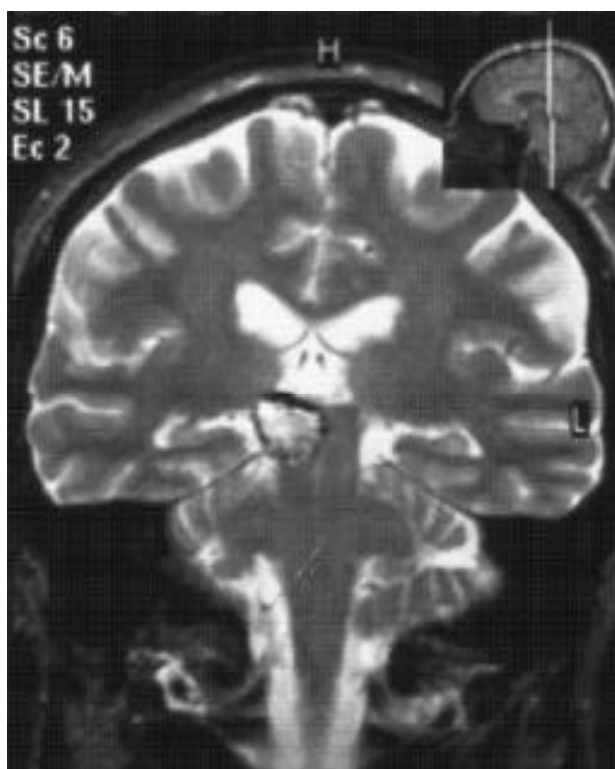
Fig. 1. Magnetic resonance imaging of cavernous angioma in the frontal lobe

A – sagittal T2-weighted fast field echo image (TR 673/TE 21, flip angle of 15°);

B – coronal T2-weighted fast field echo image (TR 802/TE 21, flip angle of 15°).



A



B

Fig. 2. Magnetic resonance imaging of cavernous angioma in the mesencephalon

A – sagittal T2-weighted spin echo image (TR 2768/TE 90);

B – coronal T2-weighted spin echo image (TR 2768/TE 90).

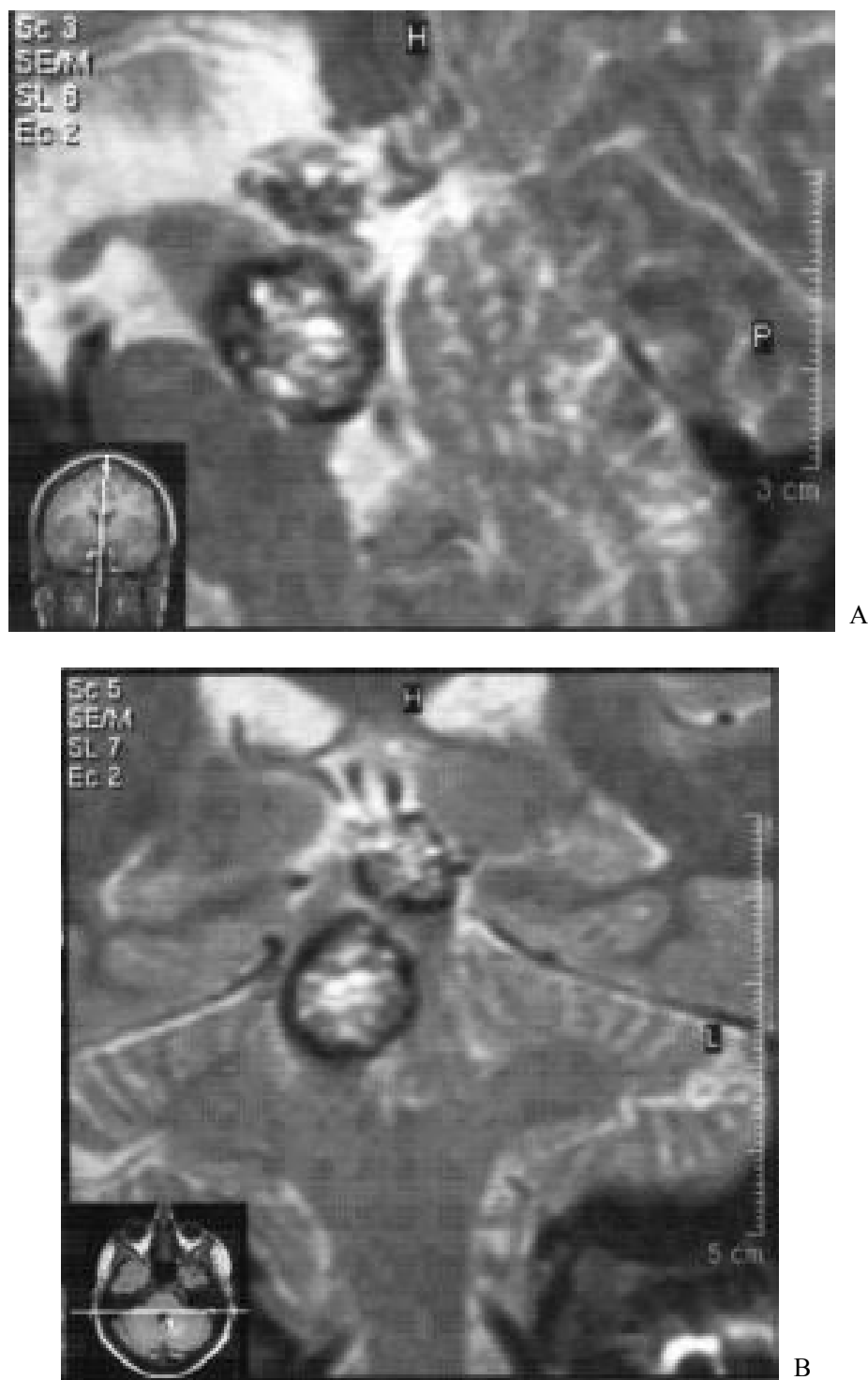


Fig. 3. Magnetic resonance imaging of multiple cavernous angiomas in the brainstem and the cerebellum

A – sagittal T2-weighted spin echo image (TR 2000/TE 90);

B – coronal T2-weighted spin echo image (TR 2000/TE 90).

those with subtentorial lesions ($P=0.0002$). There was no relationship between lesion location by cerebral lobes (occipital lobe was excluded from the analysis) and likelihood of clinical presentation by seizures ($\chi^2=0.26$; $P=0.9$). In addition, no significant diffe-

rences in the likelihood of presenting with hemorrhage between supratentorial and subtentorial lesions were found ($P=0.5$).

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

Table 2. Clinical presentation of 87 patients with cavernous angioma*

Gender	Clinical presentation			
	Headache N (%)	Seizure N (%)	Focal deficit N (%)	Hemorrhage N (%)
Male (n=41)	11 (26.8)	23 (56.1)	13 (31.7)	10 (24.4)
Female (n=46)	20 (43.5)	28 (60.9)	27 (58.7)	13 (28.3)
All patients	31 (35.6)	51 (58.6)	40 (46.0)	23 (26.4)

*Some patients presented with more than one symptom.

Table 3. Clinical presentation by lesion location in 76 patients with single lesion

Lesion location	Patients N	Clinical presentation			
		Headache N (%)	Seizure N (%)	Focal deficit N (%)	Hemorrhage N (%)
Supratentorial	64	25 (39.1)	42 (65.6)	25 (39.1)	17 (26.6)
Frontal	21	7 (33.3)	13 (61.9)	10 (47.6)	8 (38.1)
Temporal	31	11 (35.5)	20 (64.5)	8 (25.8)	5 (16.1)
Parietal	11	7 (63.6)	8 (72.7)	7 (63.6)	4 (36.4)
Occipital	1	–	1	–	–
Subtentorial	12	5 (41.7)	1 (8.3)	12 (100)	5 (41.7)
Cerebellar	5	4 (80.0)	–	5 (100)	3 (60.0)
Brainstem	7	1 (14.3)	1 (14.3)	7 (100)	2 (28.6)

*Some patients presented with more than one symptom.

There were no associations between size of cavernoma (median 1.80 for hemorrhage and median 1.55 cm for chronic seizures) and the initial presentation of cavernoma by an extralesional hemorrhage or chronic seizures ($P>0.05$).

Thirty-four (66.7%) patients with seizures had a history of chronic epilepsy and a longer mean duration of illness (1482.8 ± 126.2 days); eighteen patients had only single or sporadic seizures and a fast diagnosis of cavernous angioma and surgical treatment, so that the mean duration of illness was much shorter (76.7 ± 18.1 days). Eight patients with seizures had multiple lesions. This accounted for 72.3% (8/11) of all patients with multiple lesions in a group. The results of the preoperative neurological examination were normal in 37 patients. The other 14 had focal neurological signs. Eight patients had intracerebral bleeding, which in 5 of these 8 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 (50%) and those with sporadic seizures (40%) (Table 4). The frontal region was the second most common lesion location in both groups of patients.

According to the KPS, out of 53 patients presenting with headache, sporadic seizures, or intracerebral hemorrhage, preoperative neurological status was inferior or equal to 70 in 19 patients (35.8%) and superior or equal to 80 in 34 (64.2%). In 44 (83.0%) patients of this group, the KPS score at discharge was 80 to 90 (good outcome). Poor outcome was defined by death in 1 patient (1.9%) or a postoperative KPS inferior or equal to 70 in 8 patients (15.1%).

The mean duration of follow-up of patients with chronic seizures was 1474.0 ± 125.8 days. Postoperative focal neurological signs (sensorimotor defects) were present in 4 patients (11.8%). Of the 34 patients who underwent operation for seizure control, 27 (79.4%) reported significant seizure reduction or elimination after surgery. Six patients reported the same frequency and type of seizures as before operation. Worsening of epileptic seizures was observed in one patient (2.9%) of the group.

Discussion

In our series, most common clinical presentation of CAs was seizures, significant part of which was chronic. No association was found between lesion

Table 4. Location of cavernous angiomas in 43 patients presenting with seizures

Lesion location	Patients N	Seizures	
		Chronic N (%)	Sporadic N (%)
Supratentorial	42	27 (96.4)	15 (100.0)
Frontal	13	8 (28.6)	5 (33.3)
Temporal	20	14 (50.0)	6 (40.0)
Parietal	8	4 (14.3)	4 (26.7)
Occipital	1	1 (3.6)	–
Subtentorial	1	1 (3.6)	–
Cerebellar	–	–	–
Brainstem	–	1 (3.6)	–

location by cerebral lobes and likelihood of clinical presentation by seizures. No significant differences in the likelihood of presenting with hemorrhage between supratentorial and subtentorial lesions were detected. In addition, no associations were found between size of cavernoma and the initial presentation of cavernoma by an extralesional hemorrhage or chronic seizures. In the group of patients presenting with headache, sporadic seizures, or intracerebral hemorrhage, good postoperative outcome was achieved in 83% of the patients. Of the patients who underwent operation for seizure control, significant seizure reduction or elimination after surgery was observed in 79% of the patients.

Cavernous angiomas are considered congenital vascular hamartomas composed of closely approximated endothelial-lined sinusoidal collections without significant amounts of interspersed neural tissue. The lack of intervening neural tissue is the only histopathologic characteristic that distinguishes these lesions from capillary telangiectases. As a result, some authors have suggested that these two lesions actually represent a phenotypic spectrum within a single pathologic entity.

Most studies support equal male/female prevalence for CAs (6, 7, 10), and our results confirm these findings. Supratentorial locations of CAs account for about 80%, while other 20% are located in the posterior cerebral fossa (2, 6, 11). According to Cavalheiro and Braga (12), the frontal region is affected in 25% of cases and the temporal and parietal regions in 15% of cases each. In our series, more than 39% of lesions were located in the temporal region and more than one-third (35.3%) – in the frontal region. 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 cavernous angioma

located in the right thalamus.

According to the literature, the prevalence of multiple cavernoma varies between 3% and 50% (2–4, 13). Many estimates are likely to be inaccurate due to inclusion of those patients not examined by MRI. In our series, nearly 13% of the patients had multiple cavernomas. It has been suggested that multiple lesions are more common in females (14). Our data support this standpoint, as a vast majority of multiple cavernoma patients in our series were women, although the sample was small.

It is worth to mention that with the advent of MRI, cavernous angiomas are currently the most commonly identified brain vascular malformations. In early studies of major autopsy reports, the calculated prevalence was 0.02–0.53%. The detection of previously unidentified asymptomatic lesions by using MRI has recently raised the estimated overall prevalence to 0.45–0.9%.

Many authors have reported imaging and/or surgical evidence of an association between cavernoma and local developmental venous anomalies (15, 16). In our series, just one patient had arteriovenous malformation in addition to cavernous angioma what is much lower compared to other reports.

Cerebral cavernomas are dynamic lesions that are prone to vary in number and size over time (17, 18). The size of cavernomas reported in the literature ranges from 0.1 cm to 9 cm in their largest diameter (19). 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 (20). 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 (20, 21).

According to many previous reports, the most com-

mon manifestations of cerebral cavernomas are partial or generalized seizures, accounting for 40–70% of cases (2, 6, 7, 11). 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 (1, 2, 6). Headaches also belong to common clinical signs of CAs (22). Thus, our series is not different and fits well within the reported ranges.

Our results indicate that the excision of CAs leads to a favorable epilepsy outcome as it was pointed out by other studies (2, 23). A proportion of those seizure-free or with a marked reduction in seizure frequency was somewhat higher than that reported by Churchyard et al. (24) or by Moran et al. (2) 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 (1, 11, 25, 26). 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, 27) and possibly representing an irritating element (1, 28). 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 (20) 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 (22, 29). 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 (1, 28).

A special management challenge is created by cavernomas in the brainstem and deep brain structures. For our patients, we used suboccipital transventricular approach when cavernoma was located nearby the floor of the fourth ventricle. In case of inferior lateral pontine location of cavernoma, far lateral approach was applied. In order to remove the cavernoma located in the posterior lateral pontine, a retrosigmoid approach was used.

Conclusions

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.

Kaverninės angiomos: 87 chirurgiškai gydytų ligonių nekontroliuotas klininis tyrimas

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Raktažodžiai: kaverninė angioma, traukuliai, hemoragija, chirurginis gydymas.

Santrauka. Kaverninės angiomos išlieka vienu labiausiai diskutuojamų ir prieštaringai vertinamų neurologinės ir neurochirurginės praktikos klausimų. Šiame straipsnyje pateikiama pirminio klininio pasireiškimo, ikioperacinių klinikinių radinių, komplikacijų ir chirurgiškai gydytų ligonių, kuriems diagnozuota intracerebrinė kaverninė angioma, statistinė analizė.

Metodika. Nuo 1997 iki 2004 m. Kauno medicinos universiteto klinikų Neurochirurgijos klinikoje dėl intracerebrinių kaverninių angiomų operuoti 87 pacientai (41 vyras ir 46 moterys), kurie ir sudarė tiriamųjų grupę. Vidutinis pacietų amžius operacijos dieną buvo 42,4 metų, o vidutinė ligos trukmė – 120,5 dienos. Visiems pacientams prieš operaciją atliktas MRT tyrimas, taip pat visiems pacientams atliktas ikioperacinis ir pooperacinis klininis ištyrimas. Klinikinė eiga vertinta naudojant „Karnofski Performance Scale“. Ligos baigtys ligoniams, kuriems nustatyti pasikartojantys traukuliai, vertintos naudojant supaprastintą Engel klasifikaciją.

Rezultatai. Dažniausiai kaverninės angiomos pasireiškė traukuliais, iš kurių didžioji dalis buvo linkusios kartotis. Nerasta ryšio tarp kavernomos lokalizacijos smegenų skiltyse ir klininio pasireiškimo traukuliais. Taip pat nesiskyrė pakraujavimo rizika priklausomai nuo subtentorinės ar infratentorinės kavernomos lokalizacijos. Nerasta ryšio tarp kavernomos dydžio ir pirminio pasireiškimo kraujo išsiliejimu į smegenis ar

pasikartojančiais traukuliais. Grupėje ligonių, kuriems kavernoma pasireiškė galvos skausmais, sporadiniais traukuliais ar intracerebrine hemoragija, gera pooperacinė baigtis konstatuota 83 proc. atvejų. Pacientams, kurie operuoti siekiant pašalinti traukulus, žymus traukulių dažnio sumažėjimas ar išnykimas konstatuotas 79 proc. atvejų.

Išvada. Mikrochirurginis kaverninės angiomos ir ją supančios hemosiderino juostelės pašalinimas turi tendenciją žymiai sumažinti ar visiškai pašalinti pasikartojančius traukulus ir pagerinti pooperacinę pacientų neurologinę būklę.

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