Multimodal management in intracranial cavernous angiomas (intracranial cavernomas). An experience of 99 cases

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Abstract

Introduction. *Intracranial cavernomas are rare neurovascular lesions, met frequently in patients with anomalies of the vasculature of the encephalon and medulla. Cavernomas account for 0.02-0.53% of all intracranial lesions and approximately 8-15% of all intracranial vascular malformations. A procentage of about 10-30% of all cases show an association between cavernomas and arteriovenous malformations. Clinically, the lesions become symptomatic when their size becomes larger than 1cm. The symptoms include headache, seizures, focal neurologic deficit and last but not least hemorrhage.*

Materials and methods. *The authors present a study of 99 patients diagnosed and treated for intracranial cavernomas between January 2004 and January 2015 (11 years). The study encompasses 45 male patients and 44 female patients with ages ranging between 11 and 56, all treated at the Bagdasar-Arseni Emergency University Hospital in Bucharest, Romania.*

A large percentage of the cavernomas were supratentorial 72 cases (72.72%), while only 27 tumors were positioned in the infratentorial compartment of the skull. Regarding the position of the cavernomas, 29 of them (40.27%) were in the frontal lobe, 13 (18.05%) were in the parietal lobe, 20 (27.7%) were in the temporal lobe, while 3 were in the occipital lobe (4.16%). Infratentorial tumors affected the brainstem in 17 cases (62.9%) while 10 cases showed cerebellar implication (37.03%). There were 7 patients in which the authors described multiple cavernomas.

The clinical onset was represented by seizures in 59 cases (59.59%), hemorrhage in 20 cases (20.20%) and focal neurologic deficit in 13 cases (13.13%). The symptoms consisted of seizures in 63 cases (63.63%), focal neurologic deficit in 16 cases (16.16%) and hemorrhage in 23 cases (23.23%) while 9 cases (9.9%) were completely asymptomatic.

The authors chose to practice a conservative management for the 7 cases with multiple lesions, the 9 asymptomatic cases and 5 cases with deep positioning. In the 5 cases with deep cavernomas the patients were subjected to gamma knife stereotactic radiosurgery but only 2 patients showed response to treatment.

Results. *In the 99 patients presented by the authors, out of the 76 cases operated, a number of 57 interventions (75%) managed to completeley remove the lesion and perilesional gliosis. A number of 19 interven-*

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tions only managed to remove the tumor as perilesional gliosis was impossible to remove without lesions to eloquent areas.

Conclusions. *Intracranial cavernomas are rare lesions, usually incriminated when seizures appear. When they are asymptomatic the best option for the surgeon is to wait and see how the tumor behaves. When seizures appear in the array of symptoms of a given tumor the best prognosis is offered by lesionectomy with the removal of perilesional gliosis.*

Neuronavigation guided surgery has managed in most cases to facilitate complete removal of such tumors and to avoid postoperative defficit with the improvement of clinical results. Furthermore, neuronavigation removes the necessity of an unpleasant stereotactic frame.

When intracerebral hemorrhage occurs, surgery is mandatory and represents a neurosurgical emergency. In multiple tumors, the bleeding cavernoma must be removed. The effectiveness of Gamma Knife Surgery (GKS) is debatable.

Keywords: intracranial cavernomas, microneurosurgery, seizures, intracerebral hemorrhage, MRI, neuronavigation, Gamma Knife Surgery (GKS)

INTRODUCTION

Intracranial cavernomas are rare neurovascular lesions, met frequently in patients with anomalies of the vasculature of the encephalon and medulla. The first report on cavernomas appeared in the literature in the year 1846 and was authored by Von Rokitanski. In 1854, in a publication authored by Luschka, the gross macroscopic aspect of the malformations is described. (1) A few years later, in 1863Virchow describes for the first time the microscopic aspects of cavernomas. The first successfull removal of a cavernoma was reported by Bremer and Carson in 1890. (2)

The first overview of cavernous angiomas was provided by Dandy in 1928. (3) He described five of his own cases and collected 44 previously published cases to date that delineated typical macroscopic and microscopic features of this disease. To depict clinical manifestation of the brain cavernomas, Dandy identified basic clinical signs, e.g. predisposition to bleed and to cause focal neurological deficits, with epilepsy being the most common clinical manifestation of these lesions.

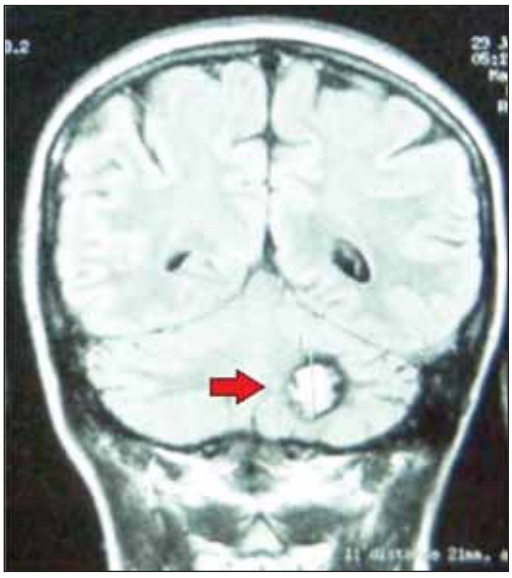
McCormik in 1966 presented a successful classification of vascular intracranial malformations in which 4 main entities were presented: Arteriovenous Malformations, Capillary Telangiectasis, Venous Angiomas and Cavernomas. (4)

Cavernomas of the central nervous system are rare neurovascular lesions usually detected in patients with ages ranging between 20 and 60. The exact pathophysiologic mechanism of appearance is not entirely known, however some genetic factors are incriminated as familial forms appear on various continents. Mutations at the level of the genes responsible for cavernoma growth generate a lesion characterized by dilated thin-walled sinusoids or caverns, covered by a single layer of endothelium that has undeveloped interstitial junctions and subendothelial interstitium. (5-12)

Cavernomas are the second most common vascular lesion in the central nervous system after venous development malformations. They account for 0.02-0.53% of all intracranial lesions and approximately 8-15% of all vascular intracranial malformations. A procentage of about 10-30% of all cases show an association between cavernomas and arteriovenous malformations.

Due to the silent nature of some cavernomas real data regarding the epidemiology of cavernomas in the general populations is impossible to achieve. Literature data states that about 68-83% of all cavernomas in the CNS are supratentorial, 15% are infratentorial (See figures 1 a&b) and only 5% have spinal implications. (14) The majority of cavernomas are located in the white substance of the cerebral hemispheres – 21% are in the frontal lobe, 16% are in the parietal lobe, 15% are in the temporal lobe, and 3.5% are in the occipital lobe. According to some authors a procentage of 10-30% of all cavernomas are positioned in the posterior fossa of the skull. Frequent locations include the cortex, the cerebellum, the brain stem and the basal ganglia, while rare locations include the ventricles (See Figures 4 a-d), the pineal area, the cranial nerves and optic chiasm, the orbits and the spine. (14)

The treatment of choice for cavernomas is almost always microsurgery due to the extreme morbidity and mortality their predisposition to recurrent hemorrhage generates. Obese fama-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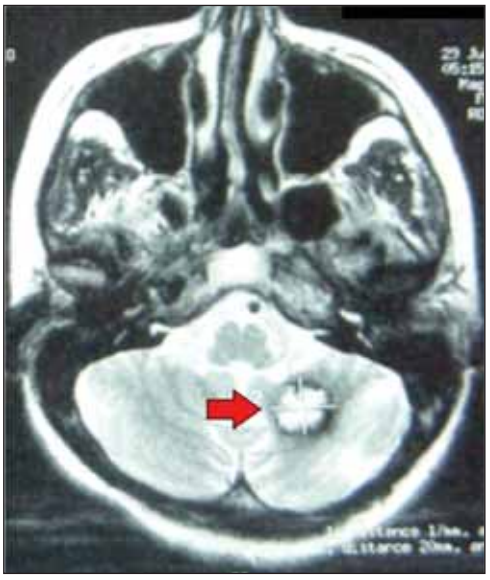
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FIGURES 1 a, b. *Computed tomography showing a cavernoma in the cerebellum of a patient*

les around the age of 40 have some of the highest rates of recurrences. (15)

There is a 0.6% rate of annual hemorrhage in patients who never had a hemorrhage before while patients who had a prior hemorrhage, have an annual rate of re-bleeding of 4.5%. There is significant data in the literature demonstrating that intracranial cavernomas represent a contraindication to pregnancy or vaginal delivery in female patients. (16-17)

The natural evolution of cavernomas is totally unpredictable and many of them remain asymptomatic in some individuals being discovered incidentally (post-traumatic CT scans). A wide series of factors are known to be risk elements in the appearance of cavernoma symptoms: arterial hypertension, stress, extreme sports, plane travel, AVM association etc.

Furthermore, haemorrhagic attacks are known to be twice as frequent in cavernomas positioned in the posterior cranial fossa and in female patients. (15)

Cavernomas of the CNS can be broadly described as clusters of enlarged anomalous blood vessels lined by a malfunctioning endothelium, bound together by a rich collagenous matrix. The endothelium lacks the presence of watertight junctions between cells as well as the support of cells such as pericytes, smooth muscle cells or astrocytic processes. The clinical translation of this aspect reflects as a malfunctioning blood-brain barrier and chronic bleeding in the surrounding tissue. The classification of cavernomas which was first made by Zabramski et al., (7) can be seen in Table 1.

TABLE 1. *Cavernoma classification after Zabramski et al. (7)*

Lesion type	MRI signal characteristics
Type IA	T1: hyperintense focus of hemorrhage T2: hyper or hypointense focus of haemorrhage extending through at least one wall of the hypointense rim that surrounds the lesion. Focal odema may be present
Type 1B	T1: hyperintense focus of hemorrhage T2: hyper or hypointense focus of hemorrhage surrouned by a hypointense rim
Type II	T1: reticulated mixed signal core T2: reticulated mixed signal core surrounded by a hypointense rim
Type III	T1: iso or hypointense T2: hypointense with a hypointensse rim that magnifies size of lesion GE: hypointense with greater magnification that T2
Type IV	T1: poorly seen or not visualised at all T2: poorly seen or not visualised at all GE: punctate hypointense

Clinically, the lesions become symptomatic when their size becomes larger than 1 cm. The increase in size translates into symptoms such as headache, seizures, focal neurologic deficit and last but not least hemorrhage which represents indication for urgent surgery due to its vital risk.

From a macroscopic point of view, cavernomas are well-defined lesions and because of their lobulated appearance often resemble a mulberry. They do not invade the neural tissue. In contrast to AVMs, large feeding arteries or draining veins are not common; therefore blood

flow inside the lesion is low. Their mean size is usually 1-2 cm, with a range from punctate to gigantic examples. The biggest lesion in our practice was 5 cm in diameter

MATERIALS AND METHODS

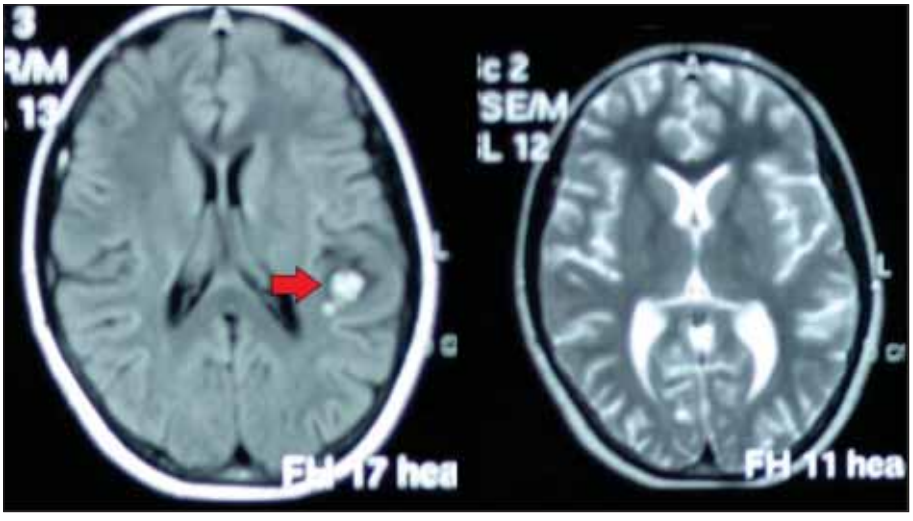
Microsurgical removal of the symptomatic cavernoma is generally accepted as the most effective and safe method. Most operated patients with a lesion in a safely accessible location usually gain convincing relief of their symptoms. Nevertheless, deep or eloquent sites of the brain in and intramedullary spine location increase surgical invasiveness and risks of postoperative complications, therefore the use of neuronavigation technology has greatly increased the quality of life of patients and improved the clinical results dramatically.

The goal of the operative treatment of a cavernoma is gross total resection. (See Figure 2, a and b) Partial removal can significantly increase the risk of bleeding with consequent complications. Total removal of the lesion requires dissection of the lesion from the surrounding brain. Thus, if the cavernoma is located within or beside critical structures of the brain (e.g. brain stem, basal ganglia, motor cortex, speech areas), any manipulation can cause mechanical or ischemic damage with concomitant dysfunctions of the affected centers.

The use of surgical microscopes and microsurgical instruments is essential in cavernoma removal. Preoperative planning and mapping of eloquent areas adjacent to the cavernoma are the most important part of the surgery, as any inaccuracy in direction of approach can lead to significant difficulties in finding small lesions within parenchyma.

The authors present a study of 99 patients diagnosed and treated for intracranial cavernomas between January 2004 and January 2015 (11 years). The study encompasses 45 male patients and 44 female patients with ages ranging between 11 and 56. Most of the patients had supratentorial cavernomas 72 cases (72.72%), while only 27 cavernomas (27.27%) were positioned in the infratentorial compartment of the skull. Regarding the position of the supratentorial cavernomas, 29 (40.27%) were in the frontal lobe, 13 (18.05%) were in the parietal lobe, 20 (27.7%) were in the temporal lobe (See Figures 3a and 3b) , while 3 were in the occipital lobe (4.16%). Infratentorial tumors affected the brainstem in 17 cases (62.9%) while 10 cases showed cerebellar implication (37.03%). There were 7 patients in which the authors described multiple tumors. In multiple cavernomas, the differential diagnosis was made with melanoma metastases, hemorrhagic metastases, aspergilloma, atrial myxoma metastases and neurocysticercosis.

The clinical onset was represented by seizures in 59 cases (59.59%), hemorrhage in 20 cases (20.20%) and focal neurologic deficit in 13 cases (13.13%). The symptoms consisted of seizures in 63 cases (63.63%), focal neurologic deficit in 16 cases (16.16%) and hemorrhage in 23 cases (23.23%) while 9 cases (9.9%) were completely asymptomatic. The authors chose to practice a conservative management for the 7 cases with multiple lesions, the 9 asymptomatic cases and 5 cases with deep positioning. In the 5 cases with deep cavernomas the patients were subjected to gamma knife stereotactic radiosurgery but only 2 patients showed response to treatment, rendering GKS Treatment debatable. (18)



FIGURES 2 a (left), b (right). *Pre- and post-op CT scans in a patient with a parietal cavernoma.*
The patient was operated using neuronavigation.

MICROSURGERY

In patients with cavernomas the craniotomy and dural opening must be always positioned exactly on the lesion site. Cortical dissection may be undertaken via a transgyral or transsulcal method as they reduce cortical lesions and expose the tumor in a „keyhole“ fashion. (19-21) The authors preffer the transsulcal approach as the major downside of the transgyral approach is the necessity to sacrifice a larger number of neurons.

On the other hand, the disruption of the arcuate fibers during transsulcal exposure is not proven to be less detrimental than disruption of vertical projection fibers after the transgyral approach. (22,23,26)

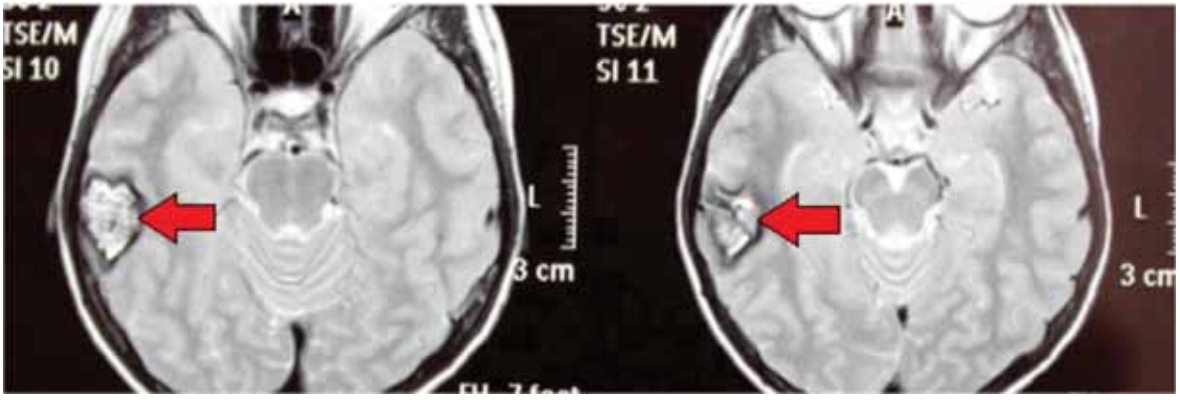
The arachnoid membrane should be dissected slowly, with extreme care regarding the vessels crossing or lying within the sulcus. It is crucial to avoid their injury as subsequent ischemia will damage the adjacent cortex. An underlying cavernoma can then be easily identified by the adjacent yellow coloration of the brain tissue.

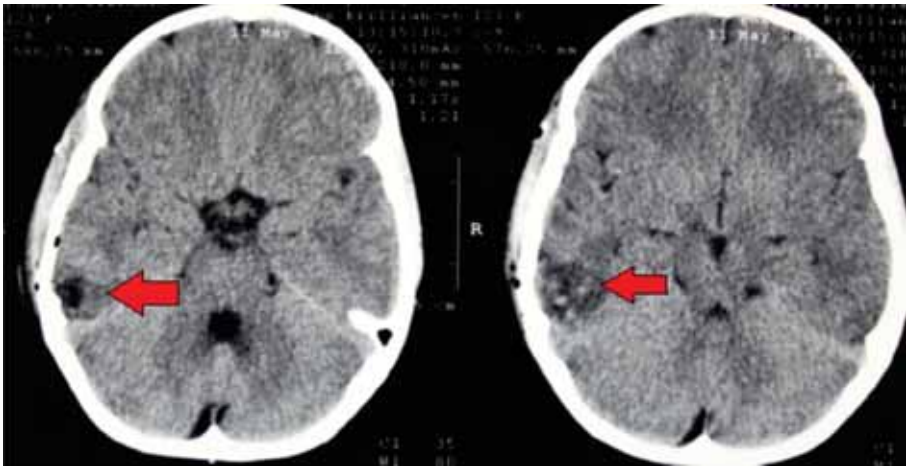
As soon as the cavernoma is identified the surgeon has to pinpoint a gliotic plane and to perform a circumferential dissection around the lesion until it is free. (19)

Extreme care must be exerted in dural-based cavernomas of the middle fossa as they often cause profuse bleeding. (19) Perilesional gliosis generated by blood breakdown products should be removed only when a lesion is located out of eloquent areas. Several studies failed to identify the impact that gliosis removal has on the remnant seizures of a cavernoma patient, however studies carried out by Hammen et al. and Baumann et al. confirmed its efficacy during long-term follow-up. (25,27-30) After exeresis of the cavernoma is carried out, a precise hemostasis is mandatory. Therefore bipolar coagulation with minimal voltage is highly recommended.

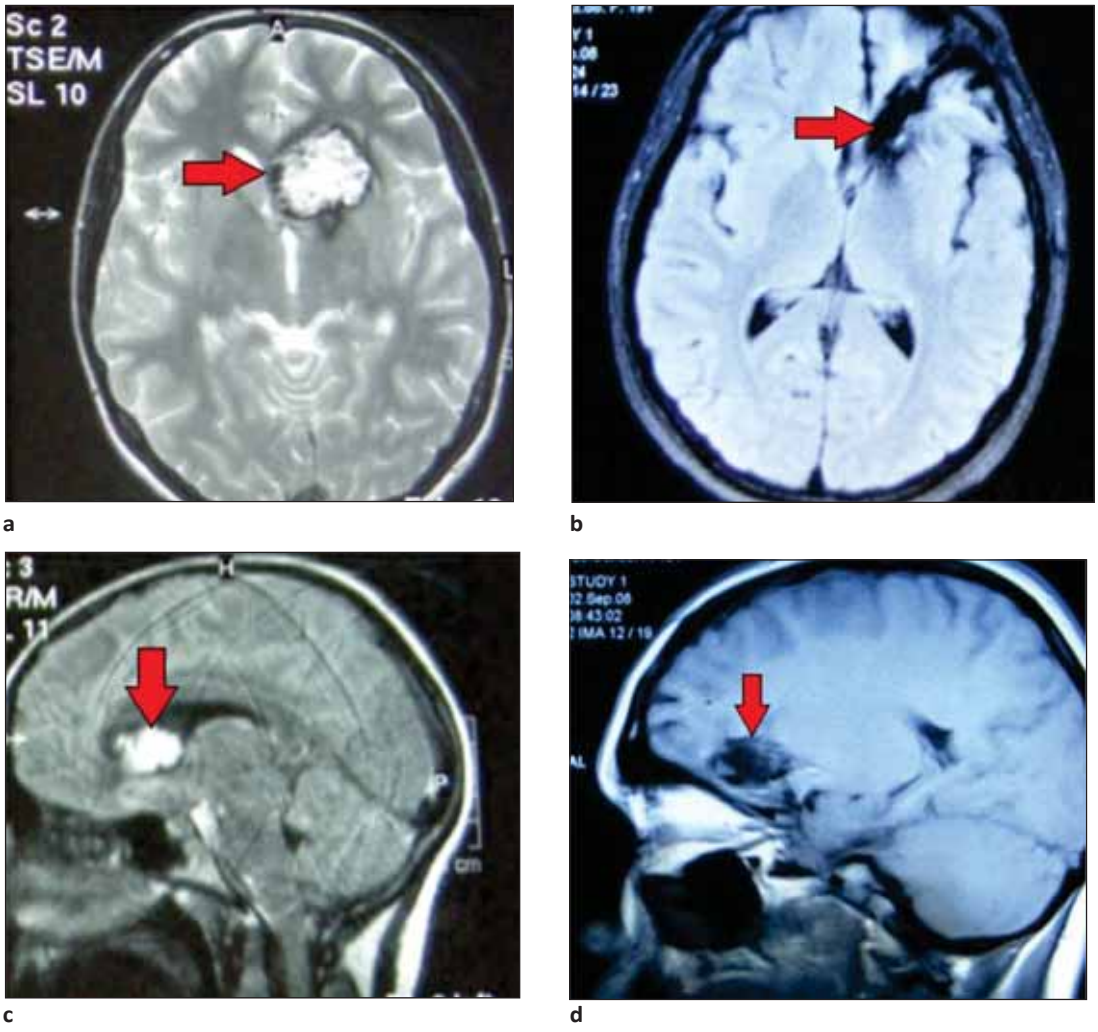
Cavernomas of the brain stem (Figure 5) are some of the most challenging neurosurgical pathologies. The decision to operate these patients should be taken only based on the existance of previous hemorrhages, the patient's neurological status, and the ability to precisely pinpoint the lesion with regard to local anatomy. (24,25)

In these situations, the lack of surgical dexterity and the most minute lesion to healthy tissue may lead to devastating outcomes. Risk of postoperative deterioration may be similar to having an overt hemorrhage from cavernoma. (26)





FIGURES 3a (upper), 3b (lower). *Pre- and post-op aspects in a temporal cavernoma*



FIGURES 4 a-d. *MRI scans showing pre- and post-op aspects of a intraventricular cavernoma*

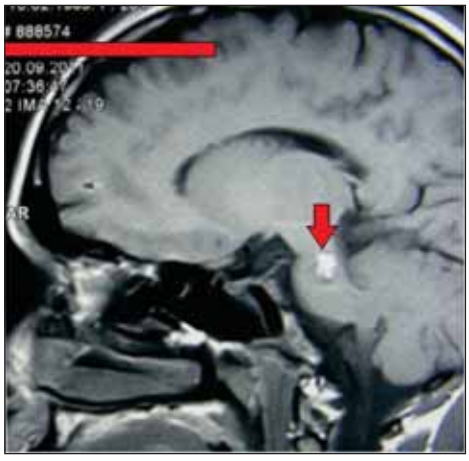
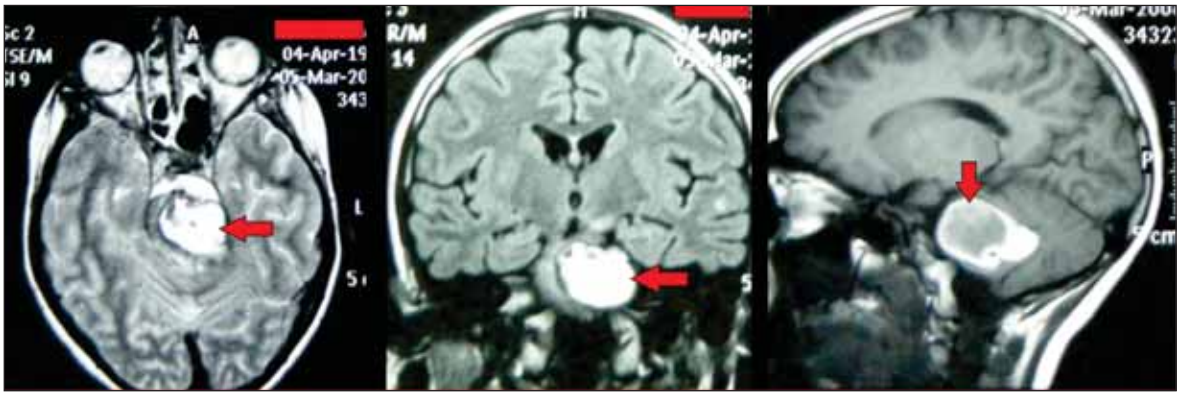


FIGURE 5. *MRI scan of a cavernoma in the brainstem*

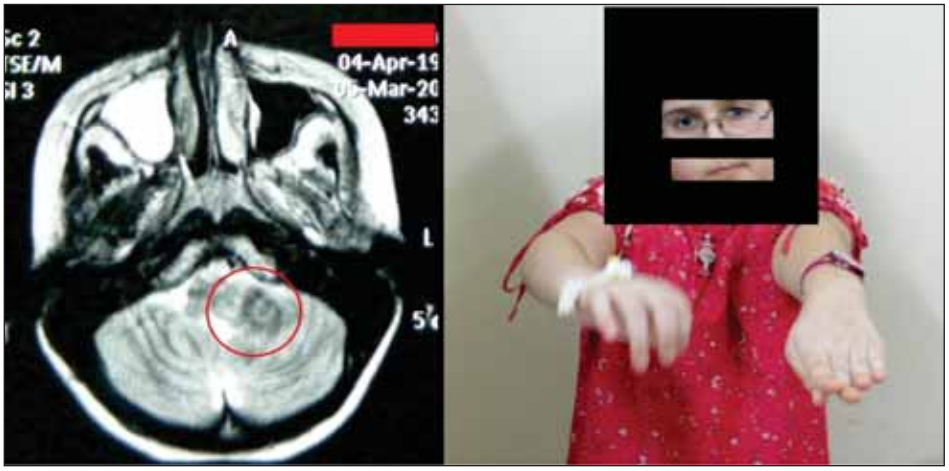
A more favorable outcome is expected when cavernomas tend to be expressed on the surface of the brainstem and the surgical gestures are reduced to a minimum. (19) Garrett and Spetzler (33), cited by Kivelev (39), recommends a supracerebellar infratentorial or lateral supracerebellar infratentorial approach for lesions involving the posterior or posterolateral midbrain. (26) To access lesions involving the anterior or anterolateral midbrain, a full or modified orbitozygomatic craniotomy is recommended. (34,35) Also, a retrosigmoid approach may grant a safe acces to lateral and anterolateral pontine lesions.

A posterior pontine and posterior medullary cavernoma abutting the floor of the fourth ventricle is best approached via a suboccipital craniotomy, whereas lateral and anterolateral medullary lesions are reached using a far-lateral suboccipital approach. (32,33,36)

Use of neurophysiologic intraoperative monitoring (IOM) and brainstem auditory evoked potentials (BAEP) during brain stem surgery is widely accepted as a remarkable adjunct to minimize surgical complications and improve outcome. (37,38) Furthermore somatosensory evoked potentials, mapping of cranial nerve nuclei, free-running electromyography, and muscle motor evoked potentials are a neurosurgeon's



From left to right: a, b, c



From left to right: d, e

FIGURES 6 a-c. *CT scan aspects of a patient with a gigantic cavernoma situated in the brainstem. Images d and e illustrate the postop results. Note that the situation of the patient was critical at admission.*

armamentarium to identify motor and sensory tracts and cranial nerve nuclei. (39-41)

IOM is needed as it allows identification of the safest entry point to the brain stem and avoids disintegration of the tracts and nuclei. However, in rare cases, false-positive and false-negative responses are observed, and the correlation between IOM and postoperative outcome may not be totally accurate. (38,42,43)

RADIOTHERAPY

In several studies, patients with higher surgical risks were considered for treatment with Gamma Knife Surgery (GKS). (39-46)

In 2010, Lunsford et al. published a study on 103 patients treated with GKS between 1988 and 2005. (51) They had noticed a convincing reduction of hemorrhage rate from 32.5% to 1.06% in two years after GKS.

Shih and Pan however, provided both GKS and microsurgery to 30 patients suffering from epilepsy and underlined an advantage of microsurgery in terms of epilepsy treatment; 79% of surgically treated patients had no seizure, whereas GKS managed to remove the seizures of only 25% of patients. (52)

Despite the above-mentioned advantages, the efficacy of GKS over the long term is debatable as the effect of GKS on intralumenal blood flow cannot be objectively confirmed by any reliable radiological investigation. Furthermore, morbidity rates range from 2.5% to 59% and mortality ranges from 0% to 8.3%(46). Radiation-induced complications include edema, necrosis, increased seizure frequency, and recurrent bleeding. (47,50)

RESULTS

The surgical results were assessed in time using native, contrast and angio MRI. In the 99 patients presented by the authors, out of the 76 cases operated, a number of 57 interventions (75%) managed to completeley remove the lesion and perilesional gliosis. A number of 19 interventions only managed to remove the tumor as perilesional gliosis was impossible to remove without vital risk.

The follow up ranges in between 6 months and 9 years, with an average timespan of 7.6 years. Follow-up protocols include a clinical examination, EEG and MRI every 6 months for the first 3 years, followed by yearly clinical assessment and MRI.

According to the Glasgow Outcome Scale (GOS) out of the 99 patients operated 75.2% showed a good recovery, 16.5% showed moderate disability, 8.2% had severe defficits. Fortunately there was no case in vegetative status or death.

CONCLUSIONS

Intracranial cavernomas are rare lesions, usually incriminated when seizures appear. When they are asymptomatic the best option for the surgeon is to wait and see how the tumor behaves. When seizures appear in the array of symptoms of a given tumor the best prognosis is offered by lesionectomy with the removal of perilesional gliosis.

Neuronavigation guided surgery has managed in most cases to facilitate complete removal of such tumors and to avoid postoperative defficit with the improvement of clinical results. Furthermore, neuronavigation removes the necessity of an unpleasant stereotactic frame. When subarachnoid hemorrhage occurs, surgery is mandatory and represents a vital emergency. In multiple tumors, the bleeding cavernoma must be removed. The effectiveness of GKS is debatable. (18,51-54)

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