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On the issue of clinical presentation, diagnostics and treatment of cavernous malformations of the brain

(literature review)

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Abstract

An analysis was made of 63 literary sources over the past 10 years, of which 16 are Russian-language and 47 are foreign, which reflect the diagnosis and treatment of cavernous malformations (CM) of the brain. When analyzing the literature data, it was revealed that cerebral CMs are the most common vascular malformations and can be found in many places in the brain. Left untreated, cavernomas can lead to intracerebral hemorrhage, seizures, focal neurological disorders, or headaches. The clinical picture and localization of the lesion are the most important factors influencing the determination of the optimal course of treatment for CM.

The purpose is to analyze and highlight the main points of the data of domestic and foreign authors regarding the etiology, pathogenesis, and classification, features of the clinical manifestations of the disease, instrumental diagnostic methods, morphology, differential diagnosis and treatment of cavernous malformations of the brain.

Despite the fact that according to the sources of literature there are numerous data concerning the clinic, diagnosis and treatment of cerebral CM, views on the diagnosis and treatment remain contradictory to date.

Keywords: Cavernous malformation (CM), brain, brain stem, subtentorial location, cerebral hemispheres, epileptic seizures.

Introduction

Cavernous malformation (KM)of the brain, known as a cavernous venous malformation, cavernous hemangioma, or cavernoma, is a common vascular disorder characterized by the presence of a system of interconnected caverns - vascular cavities of varying sizes filled with blood and separated by connective tissue, as well asThis pathology refers to the developmental defects of the vascular wallKM.

Cavernous malformation (CM) accounts for approximately 15% of all clinically manifested cases of cerebrovascular pathology, making it the second most common after arteriovenous malformations (AVM). According to autopsy data and large MRI studies, the incidence of cavernous malformations in the general population ranges from 0.1% to 0.9%. However, the proportion of this pathology in the overall structure of vascular diseases of the central nervous system is significantly higher in children, amounting to 1.7% to 42%, and in adults, from 5% to 25%. [2,3,4,5,6,8,10,12,14,20,22,23,35,41,43,51,56].

History of the study of cavernomas

The first descriptions of vascular malformations of the central nervous system appeared about 300 years ago and belong to W. Gunther ("Observation on arteriovenous malformations"). Reliable scientific data on this pathology date back to the end of the 19th century. Cavernomas were initially classified as tumors, but upon further analysis

R. Virchow came to the conclusion that these formations were a developmental defect of the vascular system of the brain. Despite Virchow's fairly definite conclusions, throughout the first half of the 20th century, clinicians and morphologists continued to discuss the issue of the origin of vascular formations of the central nervous system, not completely excluding their belonging to tumors. The removal of cavernoma was first reported by Bermer and Carson in 1890. The first review work on the surgical treatment of cavernomas was published by Dandy in 1928. In it, the author presented 5 of his own observations and 44 cases described in the literature. Eight years later, Bergstrandt et al. presented a review of data on the surgical treatment of cavernomas in a publication devoted to the results of treatment of neurovascular pathology at the Karolinska Medical Hospital. In subsequent years, the number of publications on the removal of cavernomas of various localizations began to increase rapidly. [5,6,8,10,22,23,30,35,36,63].

Etiology and pathogenesis of cavernomas

Cavernous angiomas occur in two main forms: sporadic and hereditary. The existence of familial cavernomas and the autosomal dominant type of inheritance of the pathology were proven at the stage of analysis of clinical observations. Based on the data obtained, Hayman et al. in their 1982 work were the first to show that asymptomatic forms of the disease can be detected when examining blood relatives of patients with clinically manifested cavernomas. Dubovksy and Gil-Nagel managed to localize the first of the genes responsible for the formation of cavernomas in the long arm of chromosome 7 - the CCM1 gene. Laberge-le described associated mutations of the gene causing premature cessation of protein synthesis. Subsequently, Craig et al. established the presence of two more loci associated with familial forms of cavernomas: CCM2 in the short arm of chromosome 7 and CCM3 in the long arm of chromosome 3. According to the latest data, the presence of a fourth gene (CCM4) is assumed. In recent years, the number of publications on the genetics of cavernomas has increased. The main direction of research is the study of the molecular mechanisms of cavernoma formation. By now, an idea has already been formed that the proteins encoded by the described genes "work" in close interaction, creating a complex

protein complex that ensures the morphogenesis of brain vessels and their stability. A number of gene mutations have been identified and several patterns of protein synthesis disorders have been deciphered, leading to disruption of endothelial cell formation, their migration and adhesion, which leads to the formation of cavernomas [5,,6,8,10,14,22,23,35,55,58].

Classification

Approximately 40–60% of patients with CM have a familial form, inherited in an autosomal dominant pattern due to a heterozygous mutation in one of three genes, CCM1, CCM2, and CCM3, found on chromosomes 7q, 7p, and 3p, respectively. The familial form typically results in multiple cavernomas, whereas the sporadic form typically results in a single cavernoma. CM gene products have been shown to play an important role in angiogenesis by binding to cytoskeletal proteins and interendothelial junctions in neural tissue. Loss-of-function mutations in one of these genes disrupt endothelial cell–cell junctions, resulting in extensive vascular abnormalities and increased permeability[1,2,5,6,8,10,14,22,23,35,63].

Сравнительные классификации КМ по данным МРТ

Тип	Avci E. и соавт. (2007) [4], Gross B.A. и соавт. (2013) [39]	Kim D.S. и соавт. (1997) [43]	Zabramski J.M. и соавт. (1994) [42]
I	Негомогенный гиперденсивный сигнал, в том числе с гипоинтенсивным ободком по периферии, неоднородный сигнал на Т1	Гиперинтенсивные Т1- и Т2-взвешенные МРТ указывают на наличие подострого кровоизлияния	На МРТ определяют зону повышенного сигнала в режиме Т1, характерную для подострого кровотечения
II	Встречается в 54,5% случаев, частично тромбированная с неоднородным гиперденсивным сигналом на Т1 и Т2, участками тромбоза и «старых» кровоизлияний, на КТ – включения кальция	Характеризуется разделением на полости тромбоза – кровоизлияния разных возрастов в окружении глиоза и гемосидерина. Неоднородный сигнал на Т1- и Т2-взвешенных изображениях	Признаки МРТ характерны для классической кавернозной мальформации – полости заполнены кровью, участки тромбоза различной давности, очаги кровоизлияний и отложения гемосидерина в перифокальной зоне
III	На Т1 и Т2 выявляют острую или подострую внутримозговую гематому, часто скрывающую кавернозную мальформацию, необходимо проведение повторной контрольной МРТ	Плохо визуализируется как маленький гипоинтенсивный очаг на Т1 и Т2	В режиме Т1 выявляют пониженный сигнал. В режиме Т2 очаг имеет гомогенно пониженный сигнал, что характерно для хронической гематомы в стадии резорбции
IV	Кальцифицированная (50% ее объема и более)	Острое кровоизлияние вне каверномы, как правило, приводит к прогрессирующим симптомам. Гиперинтенсивный сигнал на Т1-взвешенных изображениях	В режиме Т2 обнаруживают точечные очаги пониженного сигнала, более характерные для телеангиэктазии

МРТ – магнитно-резонансная томография, КТ – компьютерная томография

источник: статья (обзор) «Кавернозные мальформации у детей: обзор литературы» Попов В.Е., Лившиц М.И., Башлачев М.Г., Наливкин А.Е. (журнал «Альманах клинической медицины» №2, 2018)

Clinic

CMs can be found in several locations in the brain, but 70–80% of them, supratentorial CMs, most often present with new-onset seizures, but headaches are also common, while infratentorial CMs usually result in progressive neurologic deficits. Intracranial hemorrhages of varying severity can also occur in both supratentorial and infratentorial lesions. The annual risk of hemorrhage is 0.7–1.1% per lesion in patients with no history of bleeding, but increases to 4.5% in patients with a previous intracerebral hemorrhage (ICH). The risk of rupture also depends on the location of the lesion, its size, the presence of a venous malformation (VM), and the patient's gender. Superficial CMs have a lower risk of ICH than deep ones. In particular, the risk of ICH for infratentorial KMs is 3.8%, but 0.4% for supratentorial KMs. In addition, female patients have a worse prognosis than male patients [1,2,3,4,5,6,8,10,12,13,14,20,22,23,28,35,60]. The clinical course of supratentorial cavernomas, depending on their location and complexity of access, is usually divided into superficial and deep. Superficial cavernomas can be located both in functionally important areas of the brain and outside them, and deep cavernomas are located in functionally important areas. Usually, supratentorial cavernomas are detected in 80% of cases

and can have a wide range of sizes - from microscopic to giant. The localization of cavernomas is most typical in the frontal, temporal and parietal lobes of the brain (about 65%). Rare are cavernomas located in the basal ganglia and thalamus (15%), as well as in the lateral and third ventricle, hypothalamus, corpus callosum and intracranial parts of the cranial nerves. Clinical manifestations of CM depend on its location, as well as on the presence of a focus in epilepsy. The main symptoms of CM are headaches, epileptic seizures, difficulty swallowing, convulsions, coordination problems, nausea, numbness, paralysis, speech and hearing impairments, tinnitus. In chronic supratentorial localization of CM, the clinical course is often due to the appearance of small hemorrhages around the formation, which causes general or local neurological symptoms and often convulsions. Convulsions can be constant or sporadic. The main manifestation of intraventricular cavernomas is headache with nausea and vomiting. Neurological disorders can be a consequence of the development of hemorrhage [8,16,32,33,34,44,46,47,53].

Clinical course of brainstem cavernomahave a number of their own characteristics that distinguish them as a separate category of pathologies. This is due to the anatomical and functional significance of the brainstem, which makes surgical interventions in this area very complex. There are three types of pathological formations, united by the general name "brainstem cavernomas". These are subacute, chronic hematomas and typical CM in combination with acute, subacute or chronic hematoma. Even small hemorrhages from brainstem cavernomas can cause serious neurological disorders that differ from the clinical manifestations in cavernomas of other localizations. In brainstem cavernomas, two main types of clinical course are distinguished: stroke-like and pseudotumorous. The stroke-like variant is characterized by the acute development of symptoms against the background of intense headache and is usually found in hematomas of the brainstem without signs of cavernoma on MRI, while the pseudotumor variant is characterized by a slow increase in symptoms and is typical for patients with cavernomas on MRI [32,33,34,44,46,47,53].

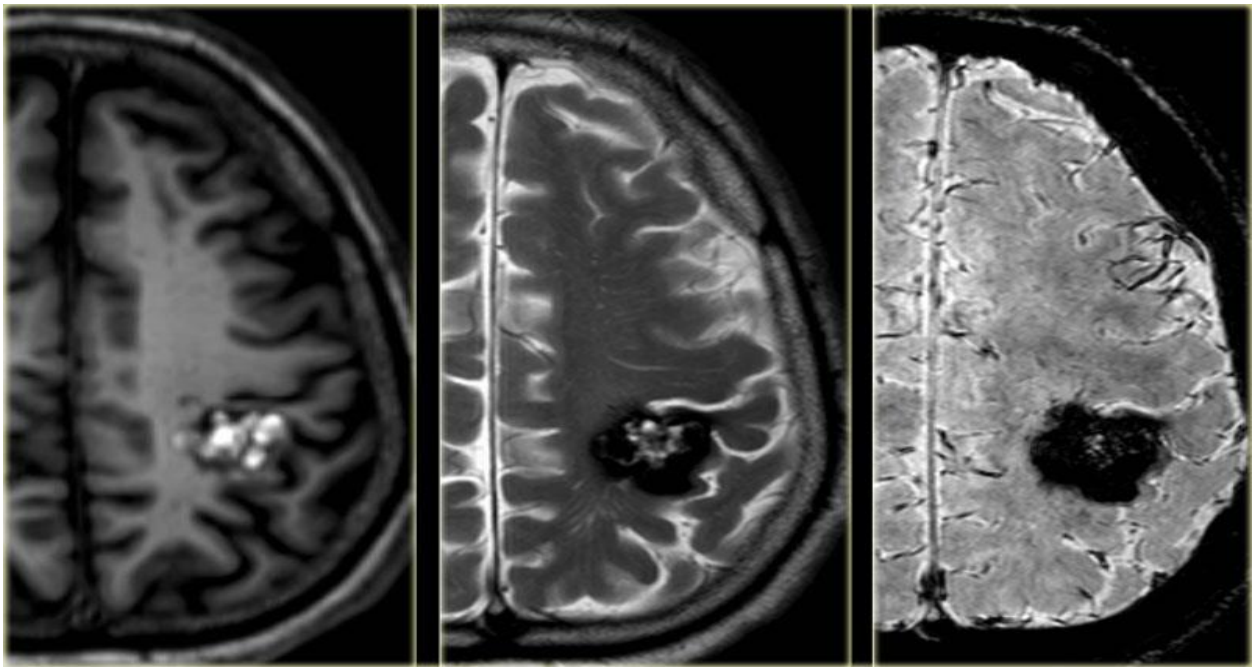
Diagnostics

The diagnosis of cavernomas is more challenging than other vascular diseases because CMs are angiographically occult malformations. Angiography can only detect the presence of abnormal venous drainage associated with the CM; therefore, other imaging modalities are needed to make an accurate diagnosis. Conventional T1- and T2-weighted MRI, gradient echo sequence, high-field MRI, susceptibility-weighted imaging, diffusion tensor imaging, and functional MRI are some of the advanced modalities that are used for the diagnosis of CMs or for intraoperative navigation during surgery. Treatment of deep lesions [3,4,5,6,7,8,10,13,14,22,23,35,50,51].

BIn the diagnosis of CM, the use of conventional 1.5 Tesla MRI is limited because CM lesions may not be visualized unless high-field MRI is used. High-field MRI is the method of choice for the diagnosis of CM because it has high sensitivity [100%] and specificity [95%] (hemoglobin degradation products such as methemoglobin, hemosiderin, and ferritin can be detected at the site of CM localization, allowing their detection by MRI[[7,26].

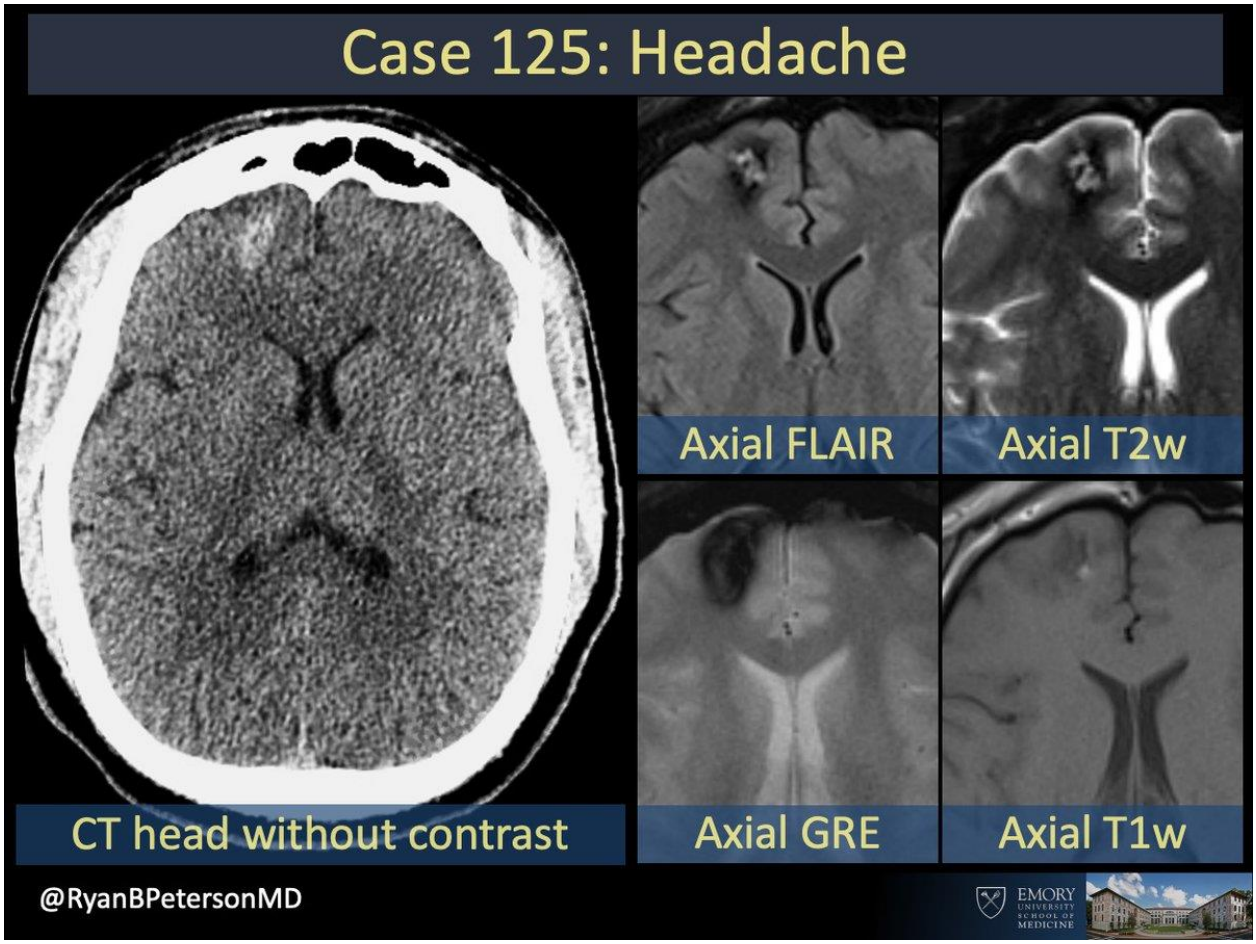
Conventional T1- and T2-weighted MRI.Conventional MRI can accurately detect symptomatic CMs that are surrounded by a ring of hypointensity due to hemosiderin deposits from recurrent microbleeds. LesionsKMare divided into four types based on their appearance on MRI. Type I lesions appear hyperintense on T1- and T2-weighted images due to a hemosiderin core from

subacute hemorrhage. Type II lesions contain focal hemorrhages surrounded by gliotic tissue, presenting a mixed signal on both T1 and T2 sequences. On T2 images, type II lesions also have a hypointense margin, resulting in a "popcorn" appearance. Type III lesions are diagnosed by the presence of an isointense core, indicating chronic resolved hemorrhage, typically seen in familial cavernous malformation. Type IV lesions are small malformations that can only be seen on gradient echo (GRE) MRI as hypointense foci and are considered capillary telangiectasias [5,6,7,8,10,22,23,31,35,37,38,57].



Gradient repeat echo (GRE) MR imaging

MRI imagingGREis a key diagnostic modality for CM due to its ability to depict hemosiderin-filled brain tissue with very distinct hypointensities. Studies of familial cavernous malformations have shown that conventional MRI detects an average of 5 lesions per patient, while T2-weighted GRE MRI detects an average of 16 lesions per patient. GREMRI not only better identifies all present lesions, but also more accurately defines their borders . Although this has several advantages, it is important to note that GREMRI increases the apparent lesion size of the CM. In addition, GRE MRI images can show multifocal lesions in elderly patients with hypertension and a history of stroke, but these should not be mistaken for familial carcinomas. They arise from hypertensive angiopathy and are localized to periventricular areas.



High Field MRIKM

The use of conventional 1.5 Tesla MRI is limited because CM lesions may not be visualized unless high-field MRI is used. High-field MRI is the method of choice for diagnosing CM because it has high sensitivity [100%] and specificity [95%] (hemoglobin degradation products such as methemoglobin, hemosiderin, and ferritin can be detected at the site of CM, allowing their detection by MRI [[7,26].

Using magnetic resonance imaging up to 1,4 Tesla, several studies have demonstrated the ability of high-field imaging to visualize lesions as hypointensities that would not otherwise be apparent. Depending on the strength of the lesions, they may appear larger than they actually are. In particular, high-field imagingat 7 Teslaresults in lesions appearing 11% larger than with traditional imaging techniques[7,26,27].

Susceptibility-weighted (SW) imagingvery useful for detecting lesionsKM, as it accurately detects deoxyhemoglobin and hemosiderin. It is also considered the only method capable of detecting non-bleeding BM lesions and telangiectasias.[7.].It has been shown thatSW-visualization allows for more precise delineation of the CM, as well as the detection of additional CM lesions that cannot be seen using conventional visualization methods.Souzaet al. studied 15 patients with familial CMs and found 5.7, 26.3, and 45.6 lesions per patient using T2-weighted imaging, T2-weighted imaging, andGRE and SW-imaging, respectively. SW imaging detected 1.7 times more lesions than T2 GRE. Other studies of familial cavernous malformations support these findings; however, SW imaging is not superior toT2 GREin relation to the detection of sporadic, singleKMor clusters of KM associated withDVA. In addition, the use of sequential SW

imaging with contrast can be very useful in distinguishing venous vasculature from small areas of hemorrhage, but this applicationSW-visualization needs further study
*Diffusion Tensor Imaging (DT) and fMRI*are used intraoperatively to better visualize lesions and surrounding parenchyma to improve surgical outcome, even if lesions are located deep in functionally significant areas[31,37,38].
Using fMRI, the process is called "diapedetic hemorrhage." The natural breakdown products of hemoglobin (hemosiderin) contained in red blood cells form a zone of chronic, specific, and highly recognizable changes on MRI around the cavernoma. Zotta et al. demonstrate the use of fMRI for surgical planning and intraoperative navigation and report higher rates of seizure freedom in patients. fMRI measures activity-dependent changes in cerebral blood flow, which becomes especially useful for resection of CM lesions located in functionally important areas of the brain.[37]

CT scan of the brain. Computed tomography (CT) reveals the following signs of CM: a hyperintense lesion with smooth contours (with calcifications) without perifocal edema and not accumulating a contrast agent. It is quite difficult to diagnose CM using CT alone. In diagnosing CM, CT can currently be used as a screening method and as a rapid method for diagnosing hemorrhage from CM when MRI is not possible.

MRI tractography. Can be used in planning the resection of deep CMs and in calculating the radiation dose in stereotactic radiosurgery. Tractography allows the surgeon to visualize the white matter tracts that often cross the hemosiderin rim of a cavernous lesion. Several studies have shown the successful use of DT imaging to localize and bypass tracts, significantly reducing the morbidity associated with CM resection.

Angiography of the CM. Despite the low information content of this research method in the diagnosis of cerebral CM, the complete exclusion of angiography from the examination of patients should be recognized as erroneous - angiography remains a necessary research method in the differential diagnosis of CM with AVM, peripheral aneurysm or vascularized tumor. It should be noted that cavernomas are filled with blood from small arterioles and capillaries, and blood outflow through venules is of the same order. Due to the small caliber of the feeding vessels, the blood pressure in cavernomas is low, so the draining veins do not hypertrophy and are not visible during CT / MRI / angiography. A characteristic feature of CM is the low blood flow velocity in them, and the contrast agent does not enter the pathological vascular formation during the short period of its passage through the vessels of the brain (CM do not accumulate or slightly accumulate the contrast agent, so most authors describe CM as a "hidden" vascular injury). In some cases, it is possible to identify an avascular zone characteristic of any volumetric formation, or, on the contrary, an unclear network of very small vessels or pathological veins [1,5,7].

Electroencephalographic examination (EEG). is performed on patients with cavernomas in cases where they suffer from epileptic seizures, as well as to confirm the epileptic nature of the paroxysms. Patients with multiple cavernomas suffering from epileptic seizures need to undergo EEG, as well as video-EEG monitoring or daily EEG monitoring to detect epileptogenic cavernoma [5,7].

Morphology of Cavernomas. Cavernous malformations have a characteristic appearance. They are rounded formations of a red-blue or brown color with an uneven, bumpy surface, clearly demarcated from the surrounding tissue. A cavernous malformation consists of caverns - cavities filled with blood at various stages of its decay. Caverns can be tightly adjacent to each other or easily separated from the main conglomerate. The size of the caverns and their relationship with the stroma can be different. The density of the formation can also be different - from soft malformations with easily torn cavern walls to dense petrified ones consisting of thrombosed cavities. The most common cavernomas are represented by multiple caverns united by loose connective tissue. The tissues surrounding the cavernoma are most often grossly altered. Yellow coloration of the brain matter, meninges or nerves is typical, indicating previous hemorrhages. This sign helps to detect cavernoma during surgical intervention. In a small number of cases, perifocal changes in brain tissue are absent.

In the immediate vicinity of the cavernoma, there is often one, or less commonly several, large pathological veins. In some cases, pathological

The vascular veins have the appearance of a typical venous angioma.

Microscopically, cavernomas are a conglomerate of thin

wall cavities of various irregular shapes, lined with endo-

telium and separated by connective tissue septa. The connective tissue septum may be represented by thin collagen fibers or coarse fibrous tissue. A characteristic feature is the absence of smooth muscle cells and elastic fibers in the walls of cavernomas, as well as brain tissue between the caverns.

Only in individual preparations can minor pro-

layers of brain tissue, which can also be found around cavernomas, completely separated from the main conglomerate. The cavities that form

cavernous, can be filled with liquid blood or blood clots in

different stages of formation. In cavernoma tissue there may be

areas of calcification and hyalinosis of the walls were detected. A common sign

is the presence in the stroma of signs of repeated hemorrhages in the form of

remnants of hematomas of varying ages. Along the periphery of the cavernoma there are often

fragments of the capsule typical of chronic can be found

hematomas [4,8,14].

Differential diagnosis

The differential diagnosis of CM should be carried out with glial tumors, thrombosed arteriovenous malformations, large and giant aneurysms, hemorrhages into the neoplasm, venous hemorrhages, melanoma metastases, toxoplasmosis and cysticercosis. In differential diagnostics with a tumor, it is possible to perform MRI with contrast enhancement, since contrast accumulation is not typical for cavernomas. In differential diagnostics with AVM and aneurysm, it is advisable to perform cerebral angiography. A false positive diagnosis of cavernoma is more dangerous than a false negative one, since there is a possibility of "missing" a disease with a life-threatening course [10,15].

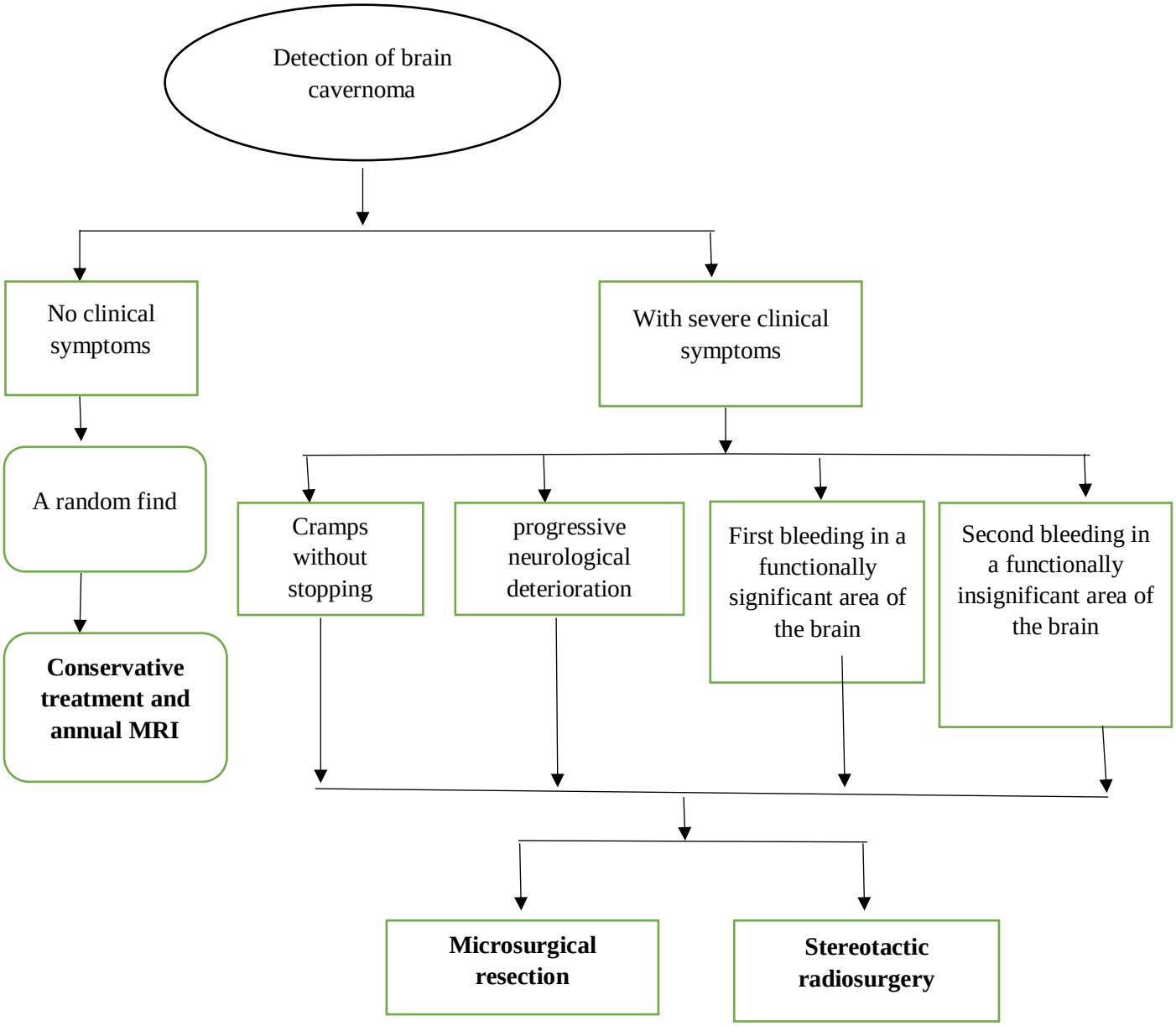
If multiple cavernomas are detected, as well as if there are blood relatives with a history of epileptic seizure(s), intracranial hemorrhage, or focal neurological deficit, it is necessary to recommend MRI examination to blood relatives to detect hereditary forms of the disease.

A final verified diagnosis of cavernoma can only be made based on the results of a histological examination. CT and AG are not methods that allow diagnosing cavernoma. They can be used as

auxiliary ones: CT to confirm the fact of acute or subacute hemorrhage, AG (SCT-AG, MRI-AG) - to identify venous angiomas, often accompanying cavernous malformations [21,29].

Treatment.*Microsurgical resection, stereotactic radiosurgery and conservative treatmentare three methods of treating CM lesions.*

Scheme of examination and management of patients with cavernous malformations.



If a brain cavernoma is detected and there are no clinical symptoms, this condition is considered a finding on MRI. These patients undergo conservative treatment, are prescribed hypotensive, antispasmodic, anticonvulsant drugs, and undergo dynamic MRI of the brain [8,10,12,13,14,18,22,23,35,50].

Conservative treatment. Once cavernomas are diagnosed by brain MRI, the choice of treatment will depend on the patient's clinical presentation. Purely incidental cavernomas are treated conservatively with annual MRI. Due to the potential risks associated with interventional treatment, several studies have been conducted on the effectiveness of medical treatment of cavernous malformations, which allows the lesions to progress naturally and only alleviates clinical symptoms. Fernandez et al. reported that surgical treatment of CM patients with epilepsy

does not significantly reduce the risk of future seizures compared with conservative treatment. They followed 17 patients treated medically for 5 years, and 12 of them (70.6%) remained seizure-free. In contrast, other studies have reported that CM patients treated conservatively have a worse long-term prognosis than those who underwent surgery (42% vs. 9%, respectively). Garrett and Spetzler studied 14 patients who were treated conservatively and found that 50% improved or remained at baseline, 29% worsened, 7% died, and 14% did not complete the study. Although some positive outcomes with conservative treatment were reported, these studies have important limitations. First of all, the number of patients studied was not large enough to represent the wide range of cases seen in the hospital. In addition, these studies were not randomized clinical trials in which patients were randomly assigned to receive surgery for various reasons, such as because they maintained good control of their epilepsy, because of the location of the CM, or simply because they refused surgery. However, this introduces bias into these studies because it is very likely that these patients had less symptomatic lesions and therefore a milder and safer natural progression than the average CM patient. Furthermore, following patients for only a few years is not sufficient, as the goal of interventional treatment is to eliminate the risk of developing any permanent neurological deficit in the long term.

Some are more skeptical of temporal clustering because there is no second period of increased risk during the 5 years of follow-up. In this case, the risk of bleeding naturally declines 2–3 years after the hemorrhage.

The decision on how to manage a patient with CM depends on many factors. Although there are many studies on each of these methods, the natural history of CM lesions is complex and not well understood, potentially challenging the conclusions drawn regarding the efficacy of the treatments used. Temporary accumulation of hemorrhage has been shown in patients with untreated CMs; 2.5 years after the first hemorrhage, a 2.4-fold decrease in bleeding was observed [16,17,60].

Surgical treatment. Cavernomas are treated with microsurgical resection or stereotactic radiosurgery if the patient has severe symptoms such as intractable seizures, progressive neurologic deterioration, one severe hemorrhage in a functionally important area of the brain, or at least two severe hemorrhages in a functionally silent area.The choice between resection and radiosurgery depends on the location of the lesion and the severity of the manifestation. When choosing a method for treating cavernoma, it is necessary to take into account that this disease is generally benign and does not pose a threat to the patient's life [4,10.12]. Treatment tactics depend on the location of the cavernoma, its size, clinical manifestations, the patient's age and concomitant diseases. Removal of the cavernoma can permanently relieve the patient of the risks associated with the disease, but does not always completely eliminate the possibility of repeated hemorrhages or epileptic seizures [16,60].

Principles of KM removal.General principles are used for surgical intervention on cavernomas of any localization, including adequate access to the malformation and the least traumatic method of its removal. Complete removal of the cavernoma is necessary, since incomplete removal can lead to repeated hemorrhages. Methods of cavernoma removal may vary depending on its localization. Currently, 2 s are usedMethod of removing KM- in one block or by fragmentation. If there is a hematoma, its removal should be the first step, as this significantly facilitates subsequent removal of the malformation [3.4, 10.12].

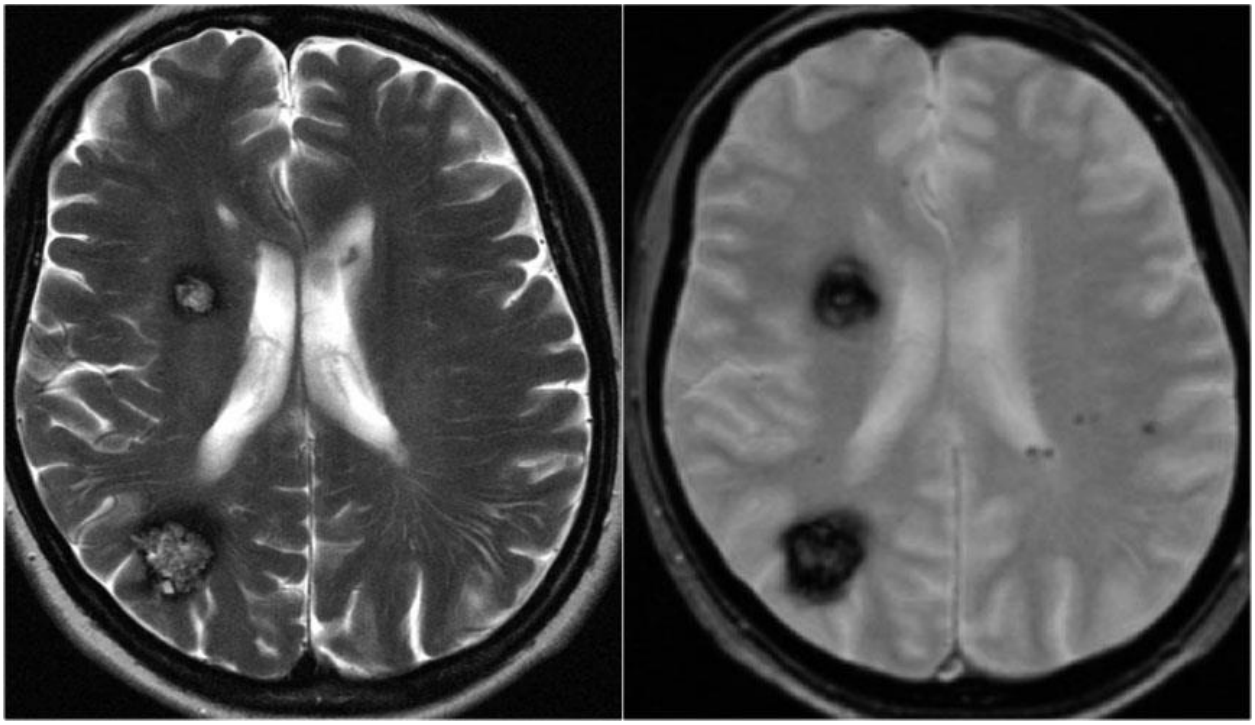
Cavernous malformations are dynamic lesions that may exhibit enlargement, regression, or even formation denovo [2,25,59]. They are resected after patients have multiple hemorrhages in functionally significant areas or a single hemorrhage in a non-reactive area associated with

worsening neurological deficit. In addition, important indications for surgical intervention include serious symptoms such as cardiac or respiratory instability, as well as the presence of a CM focus within 2 mm of the pial surface.

Patients are treated with steroids for 1-2 weeks preoperatively to limit swelling and allow CM resection. In the presence of MV associated with CM lesion, its resection should be avoided, since MV removal entails a high risk of venous infarction. Moreover, gliosis, calcification, and hyaline degeneration are common during CM lesion excision, which may complicate the procedure.

The risk of complications associated with surgery varies depending on the location of the cavernous sac lesion.[16,].Amin-Khanjani et al showed that the overall neurological status of patients was good or excellent in 100% of those with cranial nerve CMs, 97% of those with lobar CMs, 87.5% of those with cerebellar CMs, 75% of those with spinal cord CMs, and 64% of those with brainstem CMs.

Surgical ltreatment of supratentorial CM. The vast majority of CM lesions are localized supratentorially.In the presence of seizures, focal neurological deficits and headaches of supratentorial localization, symptomatic lesions of the CM, when they are located outside the FZZ of the brain, microsurgical resection is always recommended, as it has been shown to be safe and also effective in the treatment of epilepsy and the prevention of future hemorrhages. However, the decision to resect the CM becomes more difficult when the lesion is located in the FZZ of the brain and is asymptomatic or asymptomatic. When choosing a surgical approach for the treatment of a cavernous malformation of supratentorial localization, it is recommended to use the general principles of craniotomy, taking into account the localization of the CM in the brain and strive for complete removal of the CM to avoid recurrent hemorrhages. However, it should be taken into account that when cavernomas are localized in the FZZ, complete removal may lead to neurological defects.The use of frameless stereotaxy and intraoperative fMRI significantly reduces the risk of complications and makes microsurgical resection the preferred treatment for most supratentorial lesions.[12,54].Gralla et al. reported complete resection of the CM lesion using intraoperative navigation in all patients studied.

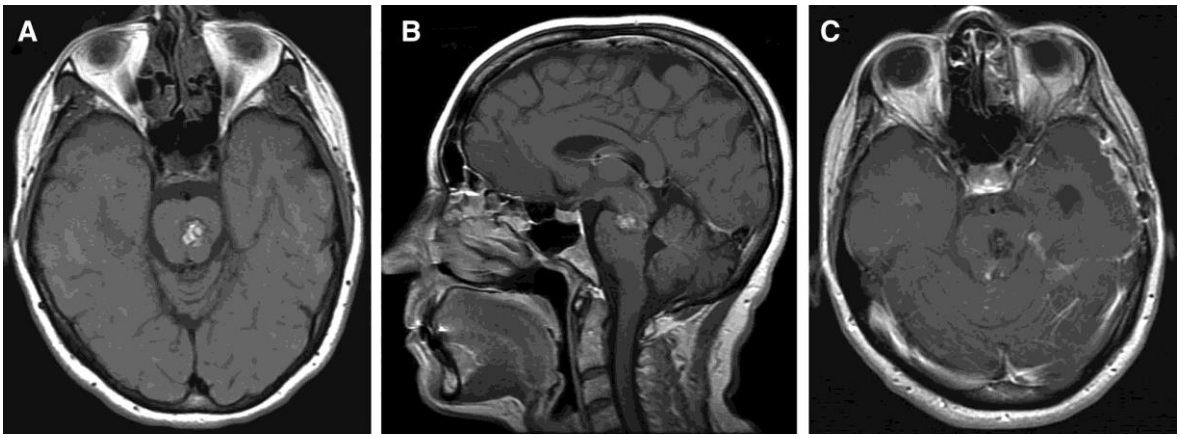


Supratentorial cavernomas.

Englot et al. studied 1226 patients with supratentorial seizures associated with CM and showed that 75% of them became seizure-free after CM resection. They also identified that total resection, surgery within 1 year of symptom onset, CM size less than 1.5 cm, and the presence of a single CM lesion were factors that significantly increased the rate of successful seizure control. In addition, Sommeretal. used intraoperative 1.5 T MRI (iMRI) and neuronavigation software for epilepsy surgery in 26 patients. They achieved complete seizure control in 80.8% of patients, which was observed over a mean follow-up of 47.7 months. The use of fMRI was significant for complete lesion resection.KMin 23% of their patients who would otherwise have had a low chance of being seizure-free. However, despite encouraging data on the effectiveness of resectionKMIn the treatment of epilepsy, antiepileptic drugs should still be the first-line therapy for epilepsy associated withKM, due to the risks of complications associated with surgery [3,5,6,8,10,14,15,22,23,28,33,34,35,43,46,52,54].

Surgical treatment of cavernomas of the trunk It is performed when a subacute or chronic hematoma is detected, there are repeated hemorrhages and the symptoms of trunk damage gradually progress.

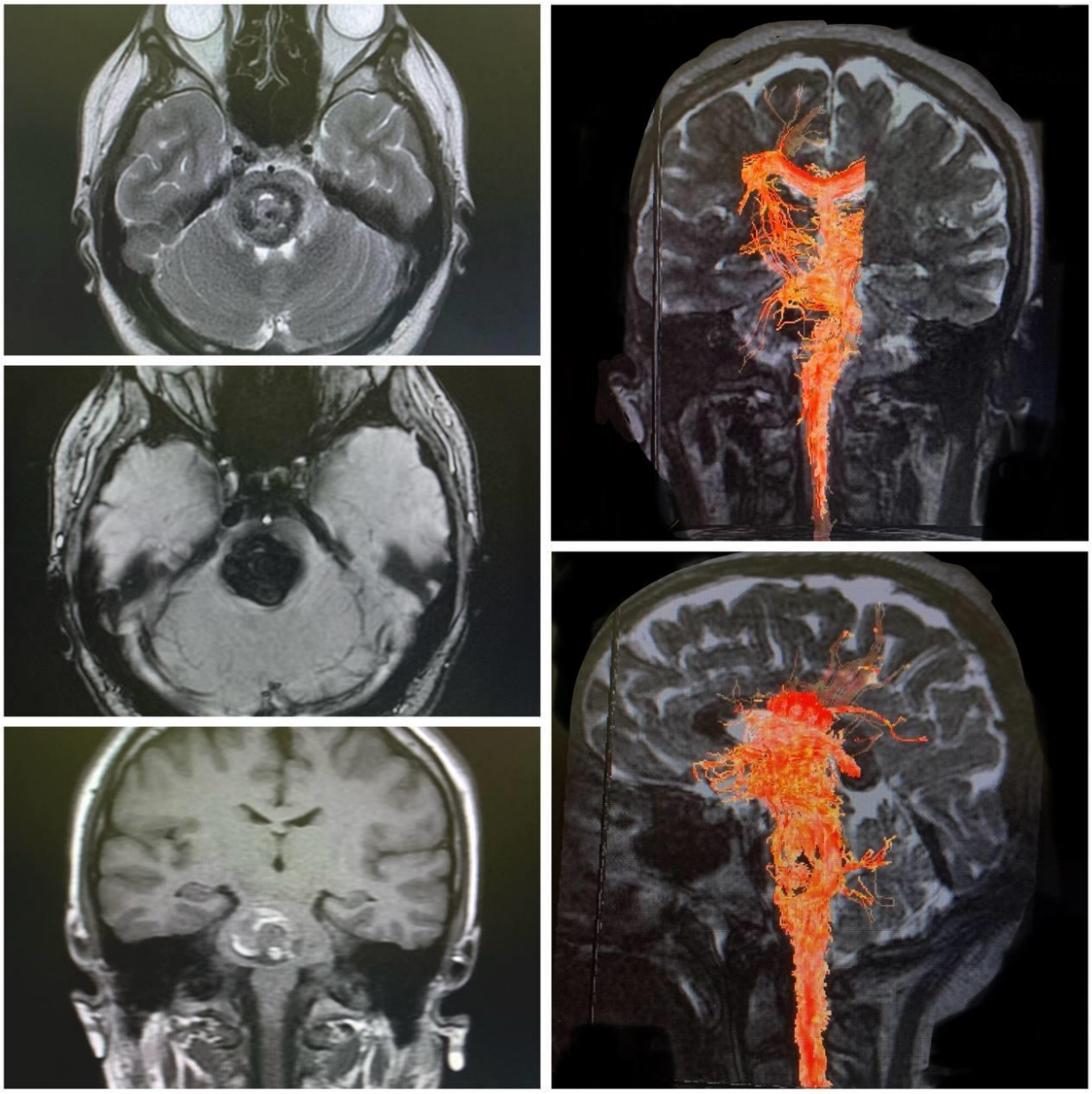
When choosing a surgical approach for the treatment of cavernous malformation of the brainstem, it is necessary to carefully study the topography of the formation using MRI. In most cases, a median suboccipital craniotomy is used, which is the most acceptable due to its ease of implementation and less trauma. However, in cavernomas and hematomas located in the ventral-lateral parts of the bridge, other approaches are more optimal, such as retrolabyrinthine, presigmoid and subtemporal, which provide a wider angle of view. An important stage of the operation is to determine the projection of the location of the cranial nerve nuclei in the bottom of the rhomboid fossa using mapping. The surgeon creates a field of view with the instruments with which he performs the operation, such as suction, tweezers, scissors, etc. It is important to radically remove the capsule of the chronic hematoma to prevent repeated hemorrhages. If the removal was incomplete, fragments of the malformation may remain, which in the future may lead to its transformation into a larger cavernoma [13,15,17,31,32,33, 34,39, 46].



BSCMs account for approximately 20–35% of all CMs and are located deep in the medulla oblongata, pons, and midbrain. The annualized risk of bleeding (AHR) for spontaneous BSCMs has been shown to be 0.25–6.5% per patient per year, while the risk increases to 3.8–35% if the patient has a history of bleeding. Some studies have reported AHRs ranging from 4.5% to 60% in patients with prior bleeding. Because of their location, BSCM hemorrhages put pressure on surrounding nuclei and cranial nerve tracts, resulting in neurologic deficits in up to 60% of patients. The blood is slowly reabsorbed, and symptoms often improve over time. Resection of BSCM lesions carries a greater risk of complications than resection of other CM lesions. This procedure has been shown to frequently cause hemorrhage-like symptoms due to increased

pressure in the brainstem, but symptoms resolve in most patients. Due to the increased risk of complications, the main criteria for selecting surgery are severe clinical presentation, including hemorrhage, and location within 2 mm of the pial surface. In cases where the lesion has severe clinical presentation but is deeply located, surgery is chosen only if the lesion is large and accessible. Frischer et al resected BSCM lesions with a mean volume of 2 cm3 when a microsurgical corridor was available [32,33,34,44,46,47,53].

There are many studies that have investigated the short-term and long-term effects of microsurgical resection in patients with BSCM lesions. In particular, Li et al. reported complete resection of the BM lesion in 95% of patients, with 35.1% of patients experiencing worse postoperative conditions. After a mean follow-up of 89.4 months, only 10.3% of patients remained in worse condition than before surgery. Frischer et al. achieved complete resection in 90% of patients and showed that 50% of patients with residual lesions experienced additional hemorrhage, resulting in a postoperative AHR of 8.8%. In a study conducted by Garrett and Spetzler on patients with BSCM lesions, the neurological status of 137 patients was examined immediately after surgery and found that 72.3% of them improved or remained the same as before surgery. After a mean follow-up of 52 months, 89.2% of them returned to their normal activities. In the same study, 88% of patients who underwent surgery were the same or better than before surgery. However, 3.5% of patients died from causes related to the surgery. In addition, 58% of their patients developed new deficits, and 12% of all treated patients had permanent deficits.



Surgical resection has been shown to be effective in the treatment of BSCM lesions, however, some studies have presented more concerning results. Abla et al showed that 7.7% of patients who underwent resection experienced rebleeding postoperatively and 36% developed persistent neurologic deficits, with surgery resolving some or all preoperative symptoms in only 45% of patients. This is illustrated by the change in mean Glasgow Outcome Score (GOS), which was 4.4 on admission, decreased to 4.2 on discharge, but increased to 4.6 at follow-up. Ferroli et al found that 44% of their patients developed new neurologic deficits postoperatively and 66% of these ultimately returned to baseline or improved from their preoperative baseline, while deficits were persistent in the remaining patients.

Precise localization of the lesion in the brainstem and the experience of the neurosurgeon are key to limiting the risk of complications and the occurrence of postoperative neurological deficit. There are large differences in the results of different studies, which may be due to the different number of patients in each study, as well as the different experience of the surgeon and the development of technology [ ].

Intraoperative neuronavigation

Using intraoperative neuronavigation techniques, diffusion tensor imaging, and fMR imaging, neurosurgeons can perform resection of deep lesions in functionally important areas of the brain with minimal new neurological deficits and low mortality and morbidity rates.

Currently, neuronavigation is used to minimize access when there are no clear anatomical landmarks at the access stage during surgical intervention, it is advisable to use this method. One of the most common methods of intraoperative navigation is ultrasound scanning, which has long been successfully used to detect volumetric formations of various natures. This method has high sensitivity and provides information in real time. However, ultrasound imaging is less effective in detecting small malformations (less than 1 cm in diameter), although the latest models of devices allow detecting increasingly smaller formations. In addition to ultrasound scanning, navigation based on preoperative MRI scans can also be used [57].

Radiosurgical treatment

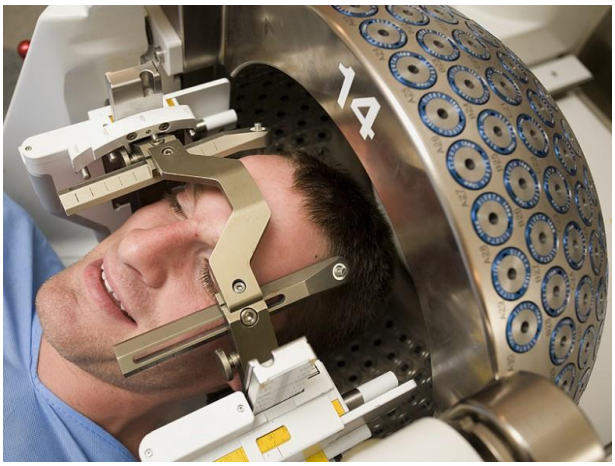
Radiosurgery is a method in which high-dose ionizing radiation is precisely directed to the target area in order to achieve the desired biological effect in this area with minimal impact on the surrounding tissues. The main goal of radiosurgery (Gamma Knife and Cyber Knife) is cavernoma obliteration by targeted exposure of the CM tissue to the effects of the radioactive beam. RX is indicated if surgical intervention is too risky, namely, in case of cavernoma of the diencephalic region, thalamus, brainstem cavernoma, multiple cavernomas, hemorrhages with the development of severe neurological deficit and in case of deep-seated small cavernomas. This method allows to avoid neurological complications, bloodless and painless treatment on an outpatient basis [9,11, 14,24,32,49, 58, 61,62].

While microsurgical resection is the standard treatment for cavernomas, the risk of complications is not insignificant when treating deep-seated, eloquent cavernomas. When surgical risk is high, stereotactic radiosurgery (SRS) can be used to prevent the natural progression of the lesion. Stereotactic radiosurgery has also advanced significantly and can be used to effectively treat inoperable cavernomas [6,8,9,11.14, ,24.32, ,49.58,61,62].

The essence of radiosurgical treatment of cavernoma is that high doses of ionizing radiation are delivered remotely to the neoplasm. Such treatment does not require the patient to be put to anesthesia, does not involve, as in the case of a surgical operation, cuts and blood, and does not carry the risk of damaging healthy structures of the brain.

Gamma Knife– one of the most modern and effective methods of treatment is a high-tech computerized device that combines the latest achievements in medical neurosurgery, radiology and robotics. Radiation from 196 Co60 sources passing through holes in the collimator helmets is directed to the selected target point and acts like a non-invasive surgical knife. At the same time, the radiation of a separate beam is not capable of having a damaging effect on the brain, but when combined at the isocenter, they create a high total dose sufficient to kill the tumor or obliterate the vascular malformation. The targeting accuracy is less than 0.5 mm, which completely eliminates irradiation of healthy brain tissue and the entire body. The first Gamma Knife operation was performed in Stockholm in 1968 on a patient with craniopharyngioma. 1972 – the Swedish company Elekta was founded. In the modern world, Elekta is the largest manufacturer of high-tech medical equipment. Gamma Knife (Lekse lGamma-Knife), linear accelerators (LINAC), diagnostic encephalomagnetography units (Neuromag), stereotactic and neuronavigation equipment (Leksell stereotactic system). Currently, about 300 Gamma Knife centers are represented and actively operating in all developed countries of the world. A significant number of devices are located in the USA (more than 100), Japan (more than 50), Russia, etc. Every year, the number of radiosurgical operations performed increases, which is

evidence of the significant effectiveness and maximum safety of this method for neurosurgical patients. It is due to the widespread introduction and use of the Gamma Knife that many patients have received the opportunity to cure various diseases, avoiding brain surgery. This method, due to its reliability and accuracy, is the "gold standard" in radiosurgery. Guidance on the target structure occurs with an accuracy of 0.5 mm in automatic mode, which completely eliminates the possible risk of errors. The mechanism of action is the defeat of tumor DNA by radiation, which accordingly leads to the death of its cells. Similar to neurosurgery, the treatment procedure is carried out once, but there is no need to perform craniotomy and skin incisions. Advantages of the method. Gamma Knife is a unique and highly accurate method that has a number of significant advantages over traditional neurosurgery. The most significant advantages include:High efficiency of the method - in 92-98% of cases after radiosurgical treatment; No need for trepanation of the patient's skull or any resections in general; Treatment is carried out in one day - the gamma knife delivers a high dose of radiation to one or more cavernomas of the brain during one treatment session; Painlessness of the procedure - local anesthesia is used at the points of contact of the stereotactic frame with the head; No need for hospitalization; The therapy is safe for nervous tissue and does not lead to neurological disorders; No need for a long recovery period, fast neurosurgical rehabilitation; No risk of bleeding and infection due to the non-invasiveness of this treatment method; Possibility of treatment of multiple formations; Possibility of safe treatment of formations located in the deep structures of the brain and on the base of the skull. The procedure takes from 10 minutes to several hours, depending on the location, size and type of pathology. Despite the safety of radiosurgical therapy, there are a number of contraindications to the treatment of CM: severe decompensated conditions, low functional status of the patient; cavernoma size more than 35 mm in diameter; presence of intracranial hypertension, severe form of cardiovascular pathologies, hydrocephalus blocking the outflow of cerebrospinal fluid, severe symptoms of compression of parts of the brain. Complications after Gamma Knife are uncommon if the selection criteria for this therapy are met. [9,17,19,40,42,44,48,53,61].



Several studies have shown that SRS is a safe and effective treatment for surgically inaccessible CM. Lunsford et al. studied high-risk CM patients treated with SRS and showed that the risk of bleeding decreased from 32.5% to 10.8% in the first 2 years and to 1% after 2 years. In the same study, 18.4% of patients experienced adverse effects from radiation; however, the percentage decreased to 8% in later patients as technology advanced. Lu et al. performed a meta-analysis that included 178 patients with brainstem CMs and they showed a significant decrease in AHR after SRS treatment. According to their data, the relative risk of hemorrhage was 0.161 (95% CI 0.052–0.493;), and 11.8% of patients developed transient or permanent neurological deficit.

Additionally, Li et al. studied the efficacy of gamma knife radiosurgery (GKRS) in patients with brainstem cavernous malformations and showed that GKRS should be considered as a treatment option for brainstem CM even in patients with only one history of hemorrhage. Park and Hwang studied 21 patients who had at least one hemorrhage due to intraaxial brainstem CM (mean 1.55 hemorrhages per patient). They followed patients for a mean of 32 months and noted that the risk of bleeding decreased from 39.5% to 8.2% after GKRS, with only one patient (5%) experiencing adverse radiation effects.

Despite the growing body of evidence supporting SRS for inoperable CM, some of the above-mentioned studies demonstrate significant radiation-induced side effects and neurological deficits as shown in Table 1. Thus, some limitations need to be noted when studying the efficacy of SRS that may affect the morbidity rate associated with SRS. Cavernoma hemorrhages typically occur as clusters with long bleeding-free intervals (temporal clusters) [8,16]. Barker II et al showed that the rebleeding rate at 1 year was 14%, but the cumulative rate increased to 56% at 5 years. Thus, the reduced risk of rebleeding observed with a mean follow-up of 32 months may be related to the bleeding-free intervals observed in CM patients.

If the cavernous malformations are small, the patient may be prescribed medication and constant monitoring of the disease. Otherwise, when it comes to a neoplasm of significant size, which may lead to serious disruptions in the functioning of the brain, even death, surgical removal of the cavernous malformation is required [5,6,8,9,10,17,19,22,23,35,40,42,44,45,48,53,61].

Surgical intervention in the brain structures in some cases of the disease can be associated with many negative factors, in particular, with a high risk of damage to healthy brain tissue. Therefore, the most effective and absolutely safe method of treating cavernoma is the CyberKnife radiosurgical system [5,6,8,7,10,11,22,23,35].

Radiosurgical system Cyber Knife

Cyber Knife. Unlike other radiosurgery methods, CyberKnife is capable of remotely, without contact with the skin, uniformly delivering a high (ablative, destroying cavernoma cells) dose of ionizing radiation directly into the volume of the malformation, without affecting healthy tissues. It should also be remembered that multiple cavernomas are detected in almost 15% of patients. Surgical treatment in this case will be even more traumatic. The accuracy of the system is determined by preliminary 3D modeling of the location of the cavernoma and healthy tissues, based on which the CyberKnife software package develops a scheme for delivering each of the many thin beams of ionizing radiation in such a way that the beams intersect as much as possible in the area of the cavernoma. The session (fraction) of radiosurgical treatment of cavernoma on CyberKnife itself lasts about 15 minutes. At this time, the patient lies motionless on a special

mobile table, and a compact linear accelerator moves around on a robotic manipulator, delivering radiation beams from the positions specified in the treatment plan. Anesthesia is not required - the treatment is bloodless and painless. The treatment is carried out on an outpatient basis - after the treatment, the patient can return to his or her normal daily routine [11].

Radiosurgical treatment of cavernoma without surgery

CONCLUSION

Cerebral cavernomas are the most common vascular anomaly, yet they are often underdiagnosed. At present, significant advances have been made in the diagnosis and treatment of CM of the brain, but the limited analysis of literature data from the last 10 years indicates that views on diagnosis and treatmentKM still remain somewhat controversial..

Using advanced imaging techniques such as T2 GRE sequences, high-field MRI and SWI imaging, we can now detect all CM lesions present in the brain.

Using intraoperative neuronavigation techniques, diffusion tensor imaging, and fMR imaging, neurosurgeons can perform resections of deep lesions in functionally important areas of the brain with minimal new neurological deficits and low mortality and morbidity rates.

Stereotactic radiosurgery has also advanced significantly and can be used to effectively treat inoperable brain cavernomas.

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