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Кавернозные мальформации головного мозга и современные взгляды на их лечение

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АННОТАЦИЯ

Кавернозные мальформации головного мозга благодаря развитию современных методов нейровизуализации являются в последние годы всё чаще обнаруживаемой патологией. Несмотря на доброкачественный характер течения в большинстве случаев, данные образования могут приводить к развитию судорожного синдрома и серьёзным неврологическим нарушениям. Как правило, причинами клинических симптомов являются кровоизлияния в структуру каверном и окружающую паренхиму головного мозга. Выбор тактики ведения пациентов с кавернозными мальформациями головного мозга зависит от типа мальформации, её размеров, локализации, наличия повторных кровоизлияний и клинической картины.

Данный обзор литературы посвящён современным методам лечения кавернозных мальформаций головного мозга, в частности хирургическим подходам. В случаях глубинного расположения очагов в функционально значимых зонах головного мозга, для которых характерен максимальный риск осложнений при хирургическом вмешательстве, альтернативными выступают методы лучевой терапии, такие как стереотаксическая радиохирургия, протонная терапия. Рассматриваются возможности, эффективность и безопасность стереотаксического радиохирургического лечения, использование протонной терапии в лечении кавернозных мальформаций. Выявлены преимущества лучевых методов лечения кавернозных мальформаций.

Ключевые слова: кавернозные мальформации; лучевая диагностика; МРТ; обзор; аппарат Гамма-нож; протонная терапия; радиохирургическое лечение; стереотаксическая лазерная абляция.

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Cavernous malformations of the brain and modern views on their treatment

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ABSTRACT

Cavernous malformations of the brain have become an increasingly common pathology in recent years, thanks to the advancement of modern methods of neuroimaging. Despite the benign nature of the course in most cases, these formations can cause convulsions and serious neurological disorders. Typically, clinical manifestations are caused by hemorrhages in the structure of the cavernous and surrounding parenchyma of the brain. The management strategy chosen for patients with cerebral cavernous malformations is determined by the type of malformation, its size, localization, the presence of repeated hemorrhages, and the clinical picture.

This literature review focuses on modern methods of treating cerebral cavernous malformations. The main methods of treatment for cavernous malformations of the brain, particularly surgical treatment, have been analyzed. If surgical intervention is not possible, alternative methods of treatment include radiation therapy, such as stereotaxic radiosurgery, and proton therapy, in cases of deep location of foci in functionally significant areas of the brain, which are characterized by the highest risk of complications. The possibilities, efficacy, and safety of stereotactic radiosurgical treatment are discussed, as well as the use of proton therapy in the treatment of cavernous malformations. Furthermore, radiation therapy has been shown to be beneficial for cavernous malformations.

Keywords: cavernous malformations; radiation diagnostics; MRI; review; Gamma knife; proton therapy; radiosurgical treatment; stereotaxic laser ablation.

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大脑海绵状畸形及其治疗的现代观点

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简评

由于现代神经影像学方法的发展，近年来大脑海绵状畸形已成为越来越可检测的病理。尽管在大多数情况下病程的性质是良性的，但这些形成可导致惊厥综合征和严重神经系统疾病的发展。基本上临床症状的原因是洞穴结构和大脑周围实质的出血。大脑海绵状畸形患者的管理策略的选择取决于畸形的类型，其大小，定位，反复出血的存在和临床情况。

这篇文献综述致力于海绵体畸形的现代治疗方法。我们分析治疗脑海绵状畸形的主要方法，特别是手术治疗。无法手术干预的时候，在大脑功能显着区域的病灶深度定位的情况下，其特征在于并发症的最大风险，放射治疗的替代方法是如立体定向放射外。同时审查立体定向放射外科治疗的可能性，有效性和安全性，使用质子治疗治疗海绵体畸形。揭示了治疗海绵体畸形的辐射方法的优点。

关键词：海绵体畸形；放射诊断；MRI；综述；伽玛刀装置；质子治疗；放射外科治疗；立体定向激光消融。

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INTRODUCTION

Cavernous malformations (CM) are vascular lesions of the brain and spinal cord with less blood supply and consist of caverns with an endothelial lining [1–4]. CMs are detected both in the supra- and infratentorial regions of the brain and less often in the spinal cord [5–8].

These lesions are the second most common vascular malformations of the central nervous system after developmental venous anomalies [9–11].

The prevalence of CM in men and women is comparable. Although CM can also be found in children, the diagnosis is usually established at age 20–40 years. In most cases, CM may not manifest clinically; however, over time, it can cause serious focal and cerebral neurological symptoms because of CM rupture and hemorrhage into the structure of the lesions and the surrounding brain tissues [12].

Although several studies have reported that the levels of risks of hemorrhages and seizures in this patient population have been established to date, a clear identification of modifiable risk factors is a significant challenge. Management of patients with CM includes monitoring or performing surgery [13, 14].

SURGICAL TREATMENT OF BRAIN CM

Microsurgical resection remains the “gold” standard of CM treatment, which can permanently relieve the patient of the concomitant manifestations of CM and the risks of developing neurological deficits associated with hemorrhages. Assessment of the risk of surgical intervention depends on the size and location of the lesion, proximity to the brain surface, and experience of the surgeon [15]. Surgical treatment is aimed at total removal of the CM and surrounding potential epileptogenic zones [16]. However, if these lesions are located close to vital structures (distance of <1 cm), complete resection can lead to postoperative neurological damage. In CMs localized in brain areas such as the thalamus, basal ganglia, or brainstem, surgery is usually performed only with frequent recurrent hemorrhages or with a significant deterioration in the patient’s condition.

Several authors note that the relatively low incidence of complications of surgical treatment exceeds the risk of hemorrhage in patients without previous diagnosis. Thus, surgical removal of asymptomatic foci, especially in cases of deep localization or localization in the brainstem, is unreasonable.

Foci that are deeply located in the basal ganglia or thalamus require a technically complex surgery, in which critical structures of the brain, including the nuclei and tracts of the white matter, can be affected; there is a risk of damage to the perforating arteries. Postoperative complications of this surgical intervention, even among experienced specialists, occur in 5%–18% of cases, and lethal outcomes occur in approximately 2% [17].

Despite the progress and improvement of surgical techniques, many patients still do not qualify for surgery or have received incomplete treatment, so CM remains untreated. As treatment for this patient population, stereotactic irradiation, such as radiosurgery and stereotactic radiation therapy, is gaining increasing significance.

POSSIBILITIES, EFFICIENCY, AND SAFETY OF RADIOSURGICAL TREATMENT OF BRAIN CM

Numerous studies have focused on the use of radiation therapy for arteriovenous malformations and dural arteriovenous fistulas [18–20]. Some studies have also demonstrated the possibility of applying this method to treat CM. Radiation therapy is mainly indicated for CM up to 3 cm in diameter and located in deep brain areas, such as those with the highest risk of complications. At present, stereotactic radiosurgical treatment is one of the main radiation therapy methods used to treat CM. Several uncontrolled studies have reported that the risk of recurrent hemorrhage after radiosurgery is reduced in patients after 2 years.

Lee et al. examined the efficacy and safety of radiosurgical treatment using the Gamma Knife in patients with brain CM [21] by analyzing the results of treatment of 261 patients with 331 symptomatic CM (average age, 39.9 years; average CM volume, 3.1 ml). The average radiation dose throughout the treatment period was 11.9 Gy. Patients were followed up for 69 months. Several patients were diagnosed with CM after an initial hemorrhage. In total, 136 hemorrhages were diagnosed before treatment.

Researchers concluded that radiosurgical treatment reduced the risk of hemorrhage in patients with CM; therefore, this method is considered an effective alternative treatment for patients with difficult surgical access or with severe concomitant diseases.

Kefeli et al. attempted to evaluate the results of treatment of brainstem CM using the Gamma Knife [22]. Their study included 82 patients with 1–3 hemorrhagic events confirmed by X-ray imaging before treatment. After the treatment, the average target volume was 0.3 ml, and the maximum radiation dose was 12 Gy. The average follow-up durations were 25.5 months before surgery and 50.3 months after surgery. The annual pretreatment hemorrhage rate was 8.6%. In the post-treatment follow-up, only three patients experienced recurrence of hemorrhage; thus, the frequency of recurrent hemorrhage within 1 year after treatment was 0.87%, i.e., the risk of such complications was significantly reduced with this therapeutic approach.

The magnitude of hemorrhage risk in CM has not been clearly defined so far. During the natural course of CM, the annual risk of hemorrhage ranges from 2.3% to 4.1%, while in surgical treatment, the risk ranges from 2.7% to 6.8%

[23, 24]. However, the risk of recurrent hemorrhage in CM increases after the initial hemorrhage, reaching 40% [25].

Wen et al. performed a meta-analysis to assess the clinical efficacy of radiosurgical treatment of CM using the Gamma Knife and revealed no significant differences in the frequency of hemorrhages between the first 2 years of the postoperative period and the subsequent 2 years (RR 2.81; 95% confidence interval 0.20–13.42) [26].

Recent studies have established an annual decrease in the frequency of hemorrhage from 39.5% to 7.2% during the first 2 years after CM treatment using the Gamma Knife and from 3.6% to 1% in subsequent years [22, 27, 28].

Kondziolka et al. studied the frequency of hemorrhages by monitoring CM and revealed that the annual frequency of hemorrhage was 5.9% before radiosurgery and 1.1% at 2 years after surgery [29]. Aboukais et al. demonstrated a decrease in this indicator from 3.16% to 2.46% [30]. Moreover, Lopez-Serrano et al. reported annual hemorrhage rates of 3.06% and 1.4% before and after radiosurgical treatment [31].

Some authors believe that the efficiency of using the Gamma Knife is apparent 2–3 years after radiosurgical treatment, which is due to a decrease in the CM volume over time caused by sclerosis and vascular thrombobliteration after irradiation [31, 32]. However, whether the decrease in the frequency of hemorrhages is associated with radiosurgical interventions or is a consequence of the natural course of CM is under discussion [21].

The assumption was that the mechanisms of radiosurgical treatment of vascular malformations are based on processes such as the proliferation of endothelial cells and hyalinization, which causes the closure of the vessel lumen. Gewirtz et al. and Nyáry et al. performed histological examinations of CM tissues in patients undergoing radiosurgical treatment, which revealed signs of fibrinoid necrosis, destruction of endothelial cells, and pronounced fibrosis in the connective tissue stroma [33, 34].

Park et al. analyzed long-term results of radiosurgical treatment of symptomatic brainstem CM using the Gamma Knife in 45 patients (14 men, 31 women) [27]. The follow-up duration was more than 5 years, with an average of 9.31 (range, 5.1–19.4) years. All patients had a history of one or more episodes of symptomatic hemorrhage before radiosurgical treatment. These hemorrhages were accompanied by manifestations of neurological deficit, including cranial nerve dysfunction, hemiparesis, hemisensory deficiency, spasticity, and chorea. The average target CM volume was 1.82 cm^3, and the median radiation dose limit was 13 Gy. Finally, the authors concluded that radiosurgical treatment with Gamma Knife is safe and clinically effective for treating CM, which reduced the recurrence rate of hemorrhage.

Until 2019, three major studies were conducted on the use of the Gamma Knife (with >100 cases and at least 4 years of follow-up) in the treatment of recurrent hemorrhagic or symptomatic CMs [35–37]. These studies enrolled a total of 530 patients. Kida showed that the annual incidence of hemorrhages after using the Gamma Knife decreased from 9.5% within 1 year to 4.7% within 2 years [37]. In other studies, the annual hemorrhage rate after treatment decreased from 15% within 2 years to 2.4% after 2 years [35].

Some researchers consider gender, severity of neurological manifestations before the intervention, CM size, degree of edema of the surrounding tissues, and radiation dose as factors that influence the frequency of hemorrhages in patients undergoing radiosurgical treatment [36]. Moreover, Kim et al. did not reveal significant differences in the frequency of hemorrhages depending on the CM volume, radiation dose, gender, and patient age at the time of treatment with the use of Gamma Knife [38].

A common complication for most patients with CM is epileptic seizures, and a correlation between the development of hemorrhages and seizures is suggested. Patients with CM often experience concomitant headaches or dizziness with hemorrhages [37]. Experimental studies have revealed that the deposition of blood clot metabolites, especially iron, can be a similar epileptogenic factor. Studies using magnetic resonance imaging (MRI) have confirmed the relationship between the development of seizures and hemorrhages in time in these patients. Another risk factor for the occurrence of seizures is the localization of the CM, primarily supratentorial, archicortical, and mesiotemporal. In comparison with MRI data, Menzler et al. demonstrated that 49 of 81 patients with CM with involvement of the cerebral cortex had seizures, while none of the 17 patients with exclusively subcortical localization of CM had seizures [39].

Considering the complications of radiosurgical treatment of CM, the risk of radiation-induced brain damage with the emergence of neurological disorders, including headache, dizziness, facial nerve palsy, facial paresthesia, diplopia, dysarthria, and asthenia in the extremities, should be noted [30]. Another serious side effect is radiation necrosis, which can promote tumor development [40].

Some researchers express concern about the ability of radiation exposure to induce the formation of new CMs, especially in children and individuals with familial illness [41].

The optimal radiation dose limit during radiosurgical treatment of brainstem CM is not clearly defined; however, Lee et al. and Kim et al. believed that the dose limit of 11 Gy is sufficient to reduce the risk of radiation complications [21, 38]. The use of a level dose is effective, while a decrease in the risk of hemorrhage to 2.4% was recorded 2 years after Gamma Knife application, including improvement in neurological status, and the rate of radiation-induced complications was 2.32%.

In general, the therapeutic dose of radiation concerning radiotoxicity in radiosurgical treatment of CM in the brainstem is 11–13 Gy [42].

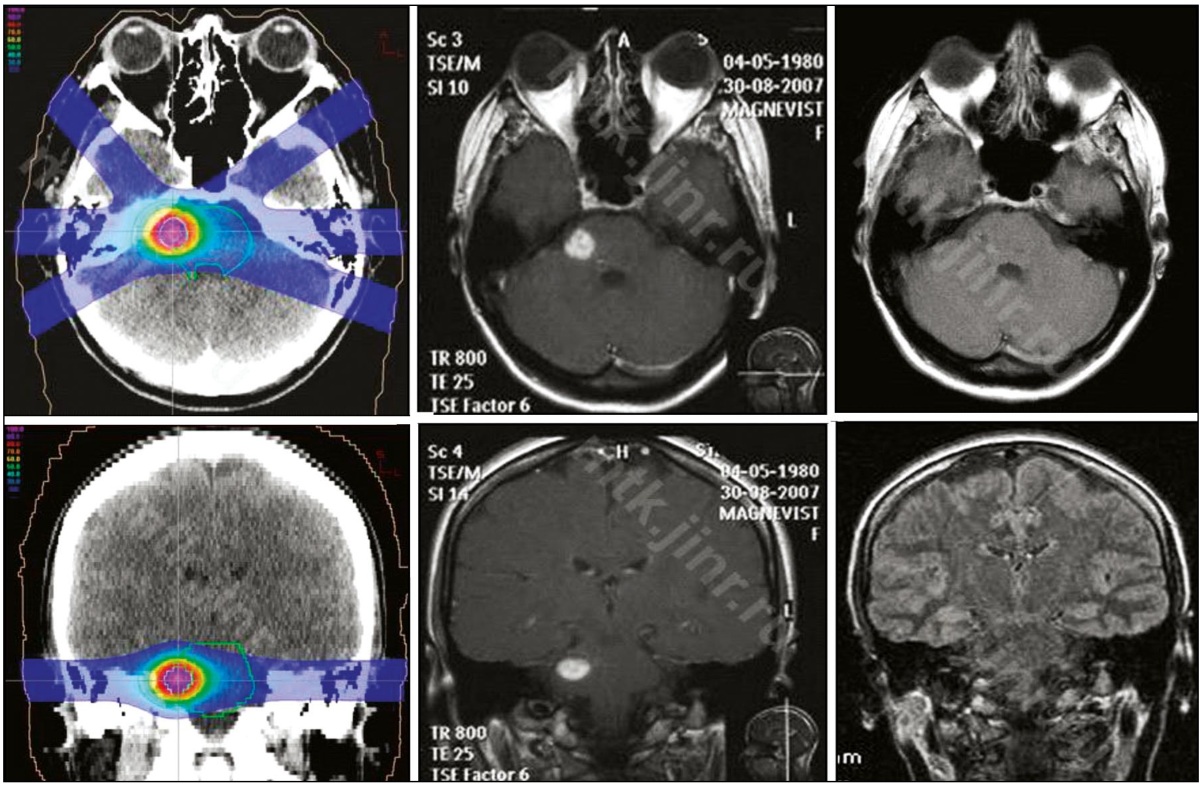

Fig. 1. Plan for proton radiosurgery of a periostemal cavernoma: contrast-enhanced magnetic resonance imaging before treatment and after 3 months showing complete resorption of the cavernoma.

Following current recommendations for radiosurgery, this approach should be considered in treating single CM in patients with a history of hemorrhage in brain areas where the surgical risk of tissue damage is unacceptably high [43]. The expert opinion is that these methods are not recommended in cases where the CM is available for surgical treatment, in asymptomatic cases, and in familial forms of the pathology.

Stereotactic laser ablation of these lesions is also considered a potentially promising method for treating CM with epileptoid manifestations [44].

Thus, radiosurgical treatment of brain CM is a relatively safe approach; as with its use, some complications, such as vascular ruptures and damage to the brain tissue, are not registered. This method implies a single provision of the entire radiation dose, which is required to obtain the desired result and is sufficiently safe for the surrounding brain matter. This approach is characterized by the highest efficiency in the treatment of CM. In some cases, the desired radiation doses cannot be used safely because of the CM size (volume), while a decrease in the dose leads to a decrease in the exposure efficiency [45].

According to Lee et al., in the past, the efficiency of radiosurgical treatment of CM was limited by insufficient capabilities of neuroimaging methods, high doses of radiation (>15 Gy), and incomplete or excessive coverage of the target area [21]. Advances in neuroimaging (such as MRI), optimization of radiation doses, and planning of interventions using appropriate software have reduced significantly the risk of complications of radiosurgery.

PROTON THERAPY IN THE TREATMENT OF CM

Proton therapy is an even more advanced method of radiation therapy when surgical removal is impossible or the patient refuses to undergo surgery. CM proton therapy, similar to stereotactic radiosurgical treatment, obliterates lesion structures and thereby reduces the risk of subsequent hemorrhages. As an advantage, proton therapy allows sufficient and accurate irradiation of the tumor (accuracy of approximately 0.5 mm) with minimal damage to healthy tissues and a decrease in the risk of side effects [46].

The treatment effect is observed within 5–90 months after application. Complete obliteration of the neoplasm is achieved in 70% of cases. The plan of proton radiosurgery of the cavernoma in the peristem is presented in Fig. 1 [47].

CONCLUSION

CMs are vascular neoplasms of the brain, which mechanism of development is based on vascular proliferation, dysmorphism, and hemorrhagic angiopathy. Clinical symptoms are caused by recurrent hemorrhages in the structure of cavernous angiomas with subsequent

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deposition of iron in surrounding brain tissues, which can result in the emergence of epileptogenesis foci, especially when the cavernomas are localized in the mesiotemporal and archicortical regions of the brain. Improvement of diagnostics and treatment methods is a multidisciplinary issue. The treatment method depends on the type, size, and location of the malformation and history of hemorrhages. Since the risk of complications of surgical intervention is high in some patients with CM and patients with a familial form of CM, improvement of alternative surgical treatment methods is extremely important. Stereotactic radiation therapy is currently increasingly used in the treatment of CMs.

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