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DIFFUSE MIDLINE GLIOMA OF THE BRAINSTEM: GENETIC FEATURES, DIFFICULTIES AND TREATMENT PROSPECTS

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Abstract
Diffuse midline glioma of the brain is a rare, but very aggressive and resistant glial tumor. This pathology is characterized by the impossibility of performing radical surgical treatment, radioresistance, unresponsiveness to drug therapy, high childhood morbidity, low quality of life of patients, frequent development of complications in the form of neurological deficit and unfavorable prognosis. The lack of an effective treatment regimen for diffuse midline glioma of the brain necessitates the search for alternative methods (virus therapy, immunotherapy), but there is insufficient data on this topic, which requires further study.
Key words: glioma, diffuse glioma, pediatric glioma, brainstem glioma, pons glioma, midbrain glioma.

Аннотация
Диффузная срединная глиома головного мозга – редкая, но очень агрессивная и резистентная глиальная опухоль. Данная патология характеризуется невозможностью выполнения радикального хирургического лечения, радиорезистентностью, невосприимчивостью к лекарственной терапии, высокой детской заболеваемостью, низким качеством жизни пациентов, частым развитием осложнений в виде неврологического дефицита и неблагоприятным прогнозом. Отсутствие эффективной схемы лечения диффузной срединной глиомы головного мозга вызывает необходимость поиска альтернативных методов (терапия вирусами, иммунотерапия), однако данных по этой теме пока недостаточно, что требует ее дальнейшего изучения.
Ключевые слова: глиома, диффузная глиома, педиатрическая глиома, глиома ствола головного мозга, глиома моста головного мозга, глиома среднего мозга.

Annotatsiya
Diffuz o‘rta joylashgan miya gliomasi — kam uchraydigan, ammo juda agressiv va davolashga chidamli glial o‘simta hisoblanadi. Ushbu patologiya quyidagi xususiyatlar bilan ajralib turadi: radikal jarrohlik davolashning imkonsizligi, nurlanishga chidamliligi, dori vositalariga javob bermasligi, bolalarda kasallanishning yuqoriligi, bemorlarning hayot sifatining pastligi, nevrologik yetishmovchilik kabi asoratlarning tez-tez rivojlanishi va noxush prognoz. Diffuz o‘rta joylashgan miya gliomasi uchun samarali davolash sxemasi mavjud emasligi sababli, alternativ usullarni (virus terapiyasi, immunoterapiya) izlash zarurati tug‘ilmoqda, biroq ushbu mavzuga oid ma’lumotlar hanuz yetarli emas, bu esa uni yanada chuqur o‘rganishni talab qiladi.
Kalit so‘zlar: glioma, diffuz glioma, pediatrik glioma, miya ustunidagi glioma, miya ko‘prigidagi glioma, o‘rta miya gliomasi.

Introduction. Diffuse brainstem glioma (DBS) of the brain was first described in 1925 by W. Harris. Today, the problem of treatment and life expectancy of patients with this pathology remains

a subject of debate, and treatment options for this disease are ineffective. According to the International Classification of Oncological Diseases, DBS was included in the group of diffuse midline gliomas due to the similarity of survival rates and response to therapy. Glial tumors are localized in the midbrain, pons or medulla oblongata, which suggests the presence of symptom complexes similar to these neoplasms [1–5]. This group includes both benign gliomas and highly malignant diffuse gliomas, characterized by rapid growth, complexity of therapy and resistance to drug treatment [3].

The incidence of DBS variants with high overall survival rates (more than 2 years) is less than 10% of cases [6]. Such tumors most often occur in children and young patients and are characterized by prolonged manifestation of symptoms [7]. Up to 90% of DGS contain a pathognomonic mutation in the H3F3A (up to 65% of tumors) and HIST1H3B (up to 25% of tumors) genes [8]. Modern clinical trials are mainly aimed at assessing radiation (RT) and/or chemotherapy (CT) using new agents, such as antiangiogenic factors, growth factor receptor inhibitors, and immunotherapy, which have proven their effectiveness in biological and preclinical studies [9, 10].

Epidemiology and molecular genetic features of diffuse midline gliomas

Diffuse midline glioma is one of the most malignant tumors of the central nervous system (CNS). Most often, it occurs in childhood. The detection rate of this pathology in all age groups is 6-7 cases per 100 thousand people per year. Almost 60% of all malignant brain tumors in children are represented by DGS. In the structure of mortality associated with brain tumors, this disease accounts for 14-16% [6, 11]. Brainstem gliomas account for about 12.5% of all CNS gliomas in children under 14 years of age and in 80% of cases are localized in the pons. The average age of disease manifestation is 7 years. The median survival after diagnosis of "malignant diffuse glioma of the brainstem" does not exceed 12 months, and for more than 30 years of observation, the life expectancy of patients with such neoplasms remains consistently low [12]. At the same time, according to some estimates, 1-, 2-, 3-, 4- and 5-year survival in all age groups is 42-44; 9-10; 4-4.5; 3–3.5 and 2.2%, respectively, i.e. 90% of patients die within the first two years [13, 14].

Malignant DGS develops from oligodendrocyte precursor stem cells. According to some data, the main factor activating oncogenesis is mutations in the H3F3A gene (K27, G34) and HIST1H3B (K27 in histone H3), which triggers the initialization and growth of tumor tissue. It was found that tumors with the H3.3K27M mutation are almost completely limited to the cerebral hemispheres and account for 16.2% of the total number of neoplasms in this localization, most often located in the parietal and temporal lobes. They develop predominantly in adolescents and young patients (median age 15 years) and are characterized by higher overall survival rates compared to other tumors with mutant variants of histone H3 (median age 18 months; 2-year overall survival 27.3%; compared with tumors with the H3.3K27M mutation; compared with tumors with the H3.1H27M mutation) [8, 15, 16]. H3.3K27M mutation variants are distributed throughout the midbrain and pons; they are found in 63% of diffuse intrinsic pontine gliomas and 59.7% of tumors of midline structures not associated with the brainstem. In all localizations, these mutations are associated with low survival rates (overall survival 11 months, 2-year overall survival 4.7%). The H3.1/3.2K27M mutation is most common in the pontine region (21.4% of cases). Tumors with this mutation are mainly detected in children and young patients (median age 5 years) and are characterized by significantly higher overall survival rates (median 15 months) compared to tumors with the H3.3K27M mutation. Multivariate analysis taking into account histone mutations, age, survival, gender, the presence of the K27M mutation in H3.3 and H3.1 demonstrated that these factors are independently associated with lower survival rates [6, 15].

Malignant DGCs often exhibit recurrent mutations in PIK3CA, TP53, PDGFRA, BRAF, and HIST1H3B, which determine tumor growth and development, resistance to treatment, and are theoretically a therapeutic target. The pK27-M mutation in histone H3 is most often found in tumor cells located in the brainstem, mainly in children (80% of cases). The ACVR1 (ALK2) missense mutation is found in 31% of cases and is reliably associated with younger patient age, longer median survival, and the presence of pK27-M, PIK3CA, or PIK3R1 mutations. The clonal activating mutation of ACVR1 is an oncogenic factor and causes the growth of malignant DGCs [17]. A gene fusion involving the kinase domain of each of the three neurotrophin receptor genes (NTRK), which is particularly common in infantile tumors, occurs in 69% of these tumors and activates RTK/RAS signaling [17, 18]. Common mutations in malignant GGS cells that contribute to tumor progression, along with K-27M, include mutations in receptor tyrosine kinases (epidermal growth factor receptors (EGFR), platelet-derived growth factor receptors (PDGFR), and fibroblast growth factor receptors (FGFR)), the WNT signaling pathway (causes excessive proliferation of atypical cells against the background of increased B-catenin), and the TP53 gene (leads to increased DNA instability, is associated with increased resistance to chemotherapy, and is found in 75% of cases). The transcription factor MYCN and its target protein PVT1 can also be overexpressed and amplified, which leads to tumor progression and recurrence. Abnormal Hedgehog signaling also plays a major role in the formation and development of malignant GGS, regardless of the presence of the K27 mutation in histone H3 [16, 19, 20]. The K27-M mutation in glial tumor cells occurs due to the replacement of the amino acid lysine 27 with methionine in histone H3 variants. The discovery of this mutation led to a change in the classification of CNS tumors by the World Health Organization: tumors with the K27-M mutation are allocated to a separate group - malignant midline gliomas. Molecular genetic studies and detection of the presence of the K27-M mutation are necessary to determine the prognosis of treatment of malignant gliomas. In tumors with the K27-M mutation, not only H3 replacement is observed, but also hyperexpression of the EZH protein and EGFR mutation. These genetic disorders can lead to loss of H3 methylation, which contributes to the oncogenesis of many CNS tumors. The exact role of the K27-M mutation in histone H3 is still not fully known, but its presence is reliably associated with a worse prognosis - a lower median survival of patients. Moreover, tumors with mutations in H3.3 are characterized by a worse prognosis compared to tumors with mutations in H3.1. Patients with malignant DGC and the K27-M mutation in histone H3, in whom the tumor is located in the projection of the thalamus, have better survival rates than those in whom the glioma is located in the brainstem or spinal cord [8, 16, 19, 21].

Surgical treatment of diffuse midline gliomas

An unfavorable prognosis in malignant DGC, regardless of the results of histological examination, has been the basis for refusing to perform surgical intervention in any volume for many years [22]. Due to the deep localization of the tumor, effective surgical treatment of these tumors is not possible. In rare cases of marginal location of the neoplasm, stereotactic biopsy can be performed to confirm the diagnosis and determine the molecular genetic status of the tumor, but this manipulation in most cases has an adverse effect on the quality of life of patients, although no direct correlation with survival rates has been identified [14, 22–24]. Currently, given the new possibilities for determining the genetic status of the tumor, which is important for predicting treatment outcomes, the neurosurgical community is leaning toward the need to perform biopsy in malignant DGS in routine clinical practice. The possibility of safe and minimally invasive material collection is a determining factor. The use of robot-assisted technologies in stereotactic biopsy demonstrates a high level of safety [24]. During a retrospective review of 22 cases of stereotactic biopsy of malignant DGS, the

development of temporary neurological disorders was noted in 15 patients, while there were no deaths. Biopsy did not negatively affect the results of therapy; The median overall survival was 10.4 ± 3.8 months [24].

Radiation therapy of diffuse midline gliomas

The most effective method of treating malignant glioma of the brainstem, given the impossibility and inappropriateness of total surgical resection, is RT (therapy with targeted ionizing radiation of high intensity). The standard approach in RT of DGS is conventional fractionation to a total focal dose (TFD) of 54–60 Gy with a single focal dose (SFD) of 1.8–2 Gy per fraction for 5–6 weeks [6, 25]. According to various authors, overall survival with this approach has not changed over the past 20 years and ranges from 11.5 to 15 months. Given the extremely unfavorable prognosis, various approaches to RT have been studied, including the use of both hyperfractionated (irradiation of the malignant tumor area with the capture of healthy tissues, 6-day course, RDA 1.17 Gy 2 times a day up to TOD 70.2) and hypofractionated (RDA 3 Gy, 5-day courses up to TOD 39 Gy, provides a median survival of up to 7.8 months) regimens. With the first approach, the median survival reaches 7.8 months, with the second - 8 months [11]. Re-irradiation is a relatively new method of treating patients with DGS. This approach can alleviate symptoms and improve the prognosis, although it is not a radical solution to the problem, but rather a palliative treatment option. Re-irradiation can be an option of choice in case of disease progression, although in rare cases it leads to an increased risk of developing neurological toxicity [26]. There are currently several studies devoted to this treatment method, but it is difficult to draw a definitive conclusion about the results of re-irradiation due to the small number of patients included in the analysis. The first and only prospective study was a phase I/II study conducted to determine the optimal dose of re-irradiation for patients with GSD. Three treatment regimens were evaluated in 12 patients: ROD 24 Gy in 12 fractions; 26.4 Gy in 12 fractions and 30.8 Gy in 14 fractions. The ROD 24 Gy in 12 fractions regimen was preferred given its safety and efficacy profile. Clinical improvement was observed in all patients except one; quality of life improved in almost 2/3 of patients (decrease in intensity and frequency of headaches, regression or absence of worsening of neurological deficit, moderate toxicity or its absence) [27, 28].

Conclusion. Today, malignant DGS with the K27-M mutation is a rare, but the most aggressive and resistant to any type of therapy tumor of the human central nervous system, characterized by a poor prognosis and extremely low quality of life of patients due to neurological deficit. This pathology occurs mainly in childhood and young age, which is a social problem. Magnetic resonance imaging remains the main method of verifying the disease, but with the development of diagnostic technologies, lumbar puncture, biopsy and molecular studies are becoming increasingly preferable options for identifying molecular therapeutic targets. The combination of RT and CT in this case should be considered as an option for tumor containment, given the low survival rates in all age and molecular groups of DGS of the brain. The use of modern molecularly based methods of exposure expands the possibilities of treating this disease. Therapies with chimeric antigen receptor T cells (CAR-T), chimeric antigen receptor NK cells (CAR-NK), and oncolytic viruses have demonstrated their effectiveness, and the study of immune mechanisms will provide new insights that will help improve the treatment of DGS.

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