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Research Status and Progress of Cerebral Glioblastoma

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Abstract: *Glioblastoma is the primary malignant tumor with the highest incidence of central nervous system in adults. Due to its high heterogeneity, strong invasiveness, blood-brain barrier and other characteristics, the therapeutic effect is not ideal, which seriously threatens the life health and safety of patients. In recent years, with the deepening of the research on the basic and clinical characteristics of glioma, the research of glioblastoma has been further developed. This article reviews the epidemiology, pathogenesis, clinical features, histopathological changes, imaging features and treatment methods of glioma in order to provide reference for the treatment of glioma.*

Keywords: *Glioblastoma; Research status; Research progress*

1. Introduction

Glioblastoma is a kind of tumor formed by the cancerous transformation of glial cells in the brain and spinal cord. Originating from neuroepithelial mesenchymal cells and neurotransmitter cells, glioblastoma can spread to brain tissues near or far from the primary lesion, and has three characteristics: highly invasive, tumor growth without clear boundaries, and infinite cell proliferation [1]. Its incidence accounts for about 50% of intracranial tumors and 81% of central nervous system malignancies [2]. It has the characteristics of high incidence, high recurrence rate, high mortality rate and low treatment rate, and the annual incidence rate is about 3-8 persons / 100, 000 population, 2-year survival rate is 26%~33%, 5-year and 10-year survival rate is only 4%~5% and 0.71%, respectively [3-4], and the 5-year mortality rate is second only to lung cancer and pancreatic cancer among systemic tumors [5-7]. Generally, the survival time of malignant brain glioma is only about 12 months, and the fatality rate is very high [8]. Over the past decades, there have been different new treatment schemes for glioma at home and abroad, and great progress has been made in surgical resection, chemoradiotherapy, targeted therapy, electric field therapy and other schemes. However, due to its characteristics of high invasion, high invasiveness and blood-brain barrier, the efficacy of existing methods has been limited, and the survival rate of glioma has not been significantly improved [9-10]. This article reviews the epidemiology, pathogenesis, clinical features, histopathological changes, imaging features and treatment methods of brain glioma, in order to provide reference for the treatment of brain glioma.

2. Epidemiology of glioma

Table 1: Classification of brain gliomas

Fractionation	Item	Content description
Low grade	Level 1	Under the light microscope, the tumor cells appear as stars, which are generally benign and can be cured
	Level 2	Under light microscope, the tumor cells were mainly oligodular cells
high-level	Level 3	The tumor cells were a mixture of astrocytes and granulocytes
	Level 4	Under light microscope, the tumor cells were ependymal cells

According to the latest WHO classification of glioma (GM), gliomas are divided into grade 1 and 2 low-grade glioma (LGG) and grade 3 and 4 high-grade glioma (HGG) according to the different degrees of malignancy, as shown in Table 1. The higher the grade, the higher the malignant degree and the more threatening the life safety of patients. Among them, glioblastoma (GBM) has the worst

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prognosis [11]. Studies have shown that despite maximum safe tumor resection, concurrent postoperative radiotherapy and temozolomide chemotherapy, and 6 cycles of temozolomide maintenance therapy, most patients still relapse within 2cm around the tumor cavity within 6-9 months after treatment [12]. Matteoni et al. [13] found that the ratio of male to female with glioma was 1.1:1. At the same time, it was found that high-grade glioma was more common in males and low-grade glioma was more common in females, which may be related to sex hormones and genes on Y chromosome.

3. Pathogenesis of glioma

The pathogenesis of glioma has not yet been clarified, and its overall prognosis is related to many factors such as patient age, general condition, tumor grade, tumor location, degree of resection, and molecular variation. Studies have shown that the uncontrolled regulation of oncogenes and tumor suppressor genes on cell cycle and apoptosis pathway is an important cause of cell carcinogenesis, and exploring the molecular mechanism of its growth and invasion may provide new ideas for elucidating its pathogenesis. Jeong et al. found that TXNDC12 gene protein could inhibit ER stress-induced apoptosis [14]. Professor Zhang Luyao's team found that silencing TXNDC12 in brain glioma cell line U251 could significantly inhibit cell migration [15]. Professor Liu Zhan's team found that lncRNADNAJC3-AS1 is highly expressed in glioma tissue cells, and targeted up-regulation of miR-3619-5p can down-regulate the level of lncRNADNAJC3-AS1, thus blocking the migration, invasion and epithelial-mesenchymal transformation of glioma cells [16]. Yin Hongfang et al. found that histone H3K27M (H3K27M) is an important molecular change in glioma, which can regulate the activity of PRC2 through multiple pathways and reduce the trimethylation level of H3K27, thus promoting the occurrence and development of glioma [17]. A number of studies have shown that [18-20] HMGB1 and its receptors play an important role in tumor immunosuppression, promoting tumor cell replication and tumor development. At present, it has been recognized by neurosurgeons that the prognosis of glioma is closely related to the pathological grade. Professor Wang Xinjun's team found a close relationship between HMGB1 and TLR4 in tumor tissues of glioma patients and the pathological grade through research, indicating that HMGB1 and its receptor TLR4 may be directly involved in the pathogenesis of glioma. To sum up, more and more genes related to brain glioma have been discovered, which is beneficial for clinicians to understand the driving factors of glioma and find new therapeutic targets, so as to improve the efficacy of brain glioma.

4. Clinical features and histopathological changes of glioma

4.1. Clinical Features

Brain glioma lacks specific clinical manifestations, mainly manifested by elevated intracranial pressure, neurological and cognitive dysfunction, seizures, etc. Intracranial pressure can cause headache, vomiting, papilledema and other occupying effects, acute intracranial pressure increase may induce brain hernia and endanger life. Glioma can directly stimulate and compress brain functional areas, causing neurological and cognitive dysfunction in the corresponding functional areas. More than half of glioma patients are accompanied by seizures due to direct tumor invasion, compression or abnormal metabolism [21].

4.2. Histopathological changes

Glioma is a general term for neuroepithelial tumors with glial cell phenotypic characteristics. The fifth edition of WHO Classification Criteria for Central Nervous System Tumors (2021) integrates the histological features and molecular phenotypes of tumors, and proposes new tumor classification criteria (see Table 2), which is an important basis for the diagnosis and grading of glioma. Histopathology provides basic morphological diagnosis of glioma, while molecular pathology provides information related to biological behavior of glioma, which directly affects treatment and prognosis [22]. Although the 2021 WHO Criteria for Classification of Central Nervous System Tumors (5th Edition) and the Committee on Molecular Information and Practice Methods for Central Nervous System Tumor Classification (cIMPACT-NOW) recommend that the pathological diagnosis of glioma should integrate histological types and related molecular markers, histopathological diagnosis remains the cornerstone of diagnosis. Molecular pathology cannot replace histopathology [21].

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Table 2: 2021 WHO Classification Criteria for Central Nervous System Tumors (5th edition)

Item	Adult diffuse glioma	Diffuse low-grade glioma in children	Diffuse high-grade glioma in children	Localized astrocyte glioma	Ependymal tumor
Standard	Astrocytoma, IDH mutant; Oligodendroglioma, IDH mutation with 1p/19q combination; Deletion type; Glioblasts, IDH wild type	Diffuse astrocytoma, MYB or MYBL1 variant; Angiocentric glioma; Juvenile pleomorphic low-grade neuroepithelial neoplasms; Diffuse low-grade glioma, MAPK signaling pathway; variant	Diffuse midline glioma, H3K27 variant; Diffuse hemispheric glioma, H3G34 mutant; Diffuse childhood high-grade glioma, H3 wild and IDH; Wild type; Infantile hemispheric glioma	Pilocytic astrocytoma; High-grade astrocytoma with hair-like features; Pleomorphic xanthoastrocytoma; Subependymal giant cell astrocytoma; Chordoid glioma; Astroblastoma with MN1 changes	Supratentorial ependymoma: Supratentorial ependymoma, ZFTA fusion positive type; Supratentorial ependymoma, YAP1 fusion positive type; Posterior fossa ependymoma: posterior fossa ependymoma, PFA group; Posterior fossa ependymoma, PFB group; Spinal ependymoma: spinal ependymoma, MYCN amplified type; Myxomillary ependymoma; Subependymal tumor

5. Imaging features of glioma

Magnetic resonance imaging (MRI) has played an important role in the diagnosis of brain glioma due to its advantages of high soft tissue resolution, clear anatomical background, absence of bone artifacts and three-dimensional imaging [23]. It was found in the study [24] that high ADC signal was obvious in low-grade glioma group, and low ADC signal was obvious in high-grade glioma group. Lesion boundary, uneven plain scan signal, space occupying effect, regional edema, cystic change, necrosis, tumor enhancement volume, and contact with subventricular region were significantly higher in high-grade glioma group than in low-grade glioma group. Low-grade gliomas are mainly characterized by low-density or low-mixed density lesion images, while high-grade gliomas are mainly mixed or high-density lesion images. Although imaging can determine the nature of glioma to a certain extent, pathological diagnosis is still the gold standard for its diagnosis.

6. Treatment of glioma

6.1. Traditional treatment

6.1.1. Surgery

At present, surgery is still the preferred treatment strategy for glioma, and the scope and degree of tumor resection are closely related to the prognosis of patients [25]. Gliomas are located in the brain parenchyma, diffuse invasive growth, lack of visible histological boundaries, it is difficult to achieve a true biological total resection. However, the general principle of surgical resection is to safely remove the tumor to the maximum extent, that is, to obtain the maximum degree of tumor removal with the minimum degree of tissue and nerve function damage [26]. Nowadays, the development of various assistive technologies has played a great role in promoting the surgical treatment of glioma. Microsurgery has further developed the methods and indications of microsurgery in brain surgery, and the tumors that were generally considered untreatable by surgery can now be relatively solved by microsurgery. At present, the localization and excision of intracranial tumor tissue under microscopic technique has gradually become a basic operation in neurosurgery. Through the application of neuronavigation system in surgical operations, the surgeon can correctly distinguish tumor boundaries and avoid surrounding important tissue structures, effectively enhance the accuracy of localization, improve the prognosis of glioma patients, and reduce the recurrence rate [27-28]. It shows that technical tumor resection is the emerging research direction at present. It uses fluorescein or bioenzyme to label tumor tissue, and distinguishes the specifically labeled glioma cells under fluorescence microscopy, and then determines the tumor boundary. Studies have shown that [29] the specificity and sensitivity of cerebral gliectomy under the color rendering technique are significantly higher than that of ordinary surgery, and at the same time, postoperative complications are reduced.

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6.1.2. Radiotherapy

Radiotherapy is an important treatment for glioma, including conventional radiotherapy, stereotactic radiotherapy, conformal radiotherapy, precision radiotherapy and interstitial radiotherapy. With the increasing improvement of imaging technology, radiotherapy has gradually changed from whole brain radiotherapy to local radiotherapy, and optimizing local radiotherapy is the main focus of radiotherapy research, with the ultimate goal of minimizing radiation damage in the near future while suppressing tumor progression [30]. Due to differences in the sensitivity of glioma cells to radiation therapy, the effect of radiation therapy has its own limitations, and the benefit of radiation therapy is only to kill radiation sensitive cells. Tumors are also resistant to radiation doses, and radiation therapy can only kill sensitive tumor cells, and the remaining cells can still relapse.

6.1.3. Chemotherapy

Postoperative chemotherapy is also one of the important means of glioma treatment, which is of great significance for preventing recurrence. However, due to the blood-brain barrier, tumor heterogeneity and drug resistance, the chemotherapy effect is not ideal. In recent years, with the development of new chemotherapy drugs and chemotherapy research mechanisms, the status of glioma chemotherapy has been continuously improved. Nitrosylurea drugs such as camustine and lomustine were first applied clinically, but studies have found that 06 methylguanine-DNA (MGMT) can repair DNA alkylation damage, which is the main reason for the resistance of malignant glioma cells to nitrosylurea commonly used in chemotherapy [31]. In recent years, the emergence of new alkanizing agents such as temozolomide (TMZ) has improved the chemotherapy effect of glioma patients. TMZ is a derivative of imidazole and tetrazine, which has small molecular weight, good lipophilicity, and easy to enter cerebrospinal fluid through the blood-brain barrier, and can achieve effective drug concentration in the central nervous system. With small adverse reactions and good long-term drug tolerance, it has become an effective drug in the treatment of glioma [32]. At present, studies have found that anti-cancer antibiotics, hormones, platinum, enzyme inhibitors, etc. inhibit or kill tumor cells in different links, so they may become new drugs for the treatment or adjuvant treatment of brain glioma. Studies on epirubicin, Sirolimus and cisplatin alone or in combination with other methods for the treatment of glioma have made corresponding clinical progress [33-34].

Radical surgery combined with chemoradiotherapy is the basic means to treat glioma, but due to its easy recurrence and high mortality, the therapeutic effect is not optimistic. In recent years, with the continuous research and understanding of glioma, many new therapeutic methods such as gene therapy, immunotherapy and molecular targeted therapy have been proposed.

6.2. Novel treatment modalities

6.2.1. Molecular targeted therapy

Molecular targeted therapy mainly targets specific molecules on some special conduction pathways on tumor tissues or tumor cells, making them targets that can bind specifically to some antibodies or ligands, and ultimately killing brain glioma cells [35]. At present, molecular diagnosis has become the standard to distinguish brain tumors, and molecular research has also promoted the development of glioma targeting drugs. The representative genetic alterations in gliomas are as follows: O6-methylguanine-DNA methyltransferase, isocitrate dehydrogenase (IDH1 and IDH2) and 1p/19q, epidermal growth factor receptor, telomerase reverse transcriptase gene, phospholipase and tensin homology [36]. With the progress of sequencing technology, people have a deeper understanding of the genome of glioma, and have a new understanding of the formation, diagnosis, treatment and prognosis of glioma. With the advancement of genomics technologies such as high-throughput sequencing and spatial transcriptome analysis in the future, highly specific therapeutic targets in glioma may be screened out, and the identification of new targetable and operable glioma driver genes is expected to achieve further application of targeted therapy [36].

6.2.2. Immunotherapy

In recent years, the rise of immunotherapy has provided a new idea for the treatment of glioma. Immunotherapy includes active and passive immunization. Active immunity is a method to enhance the established but imperfect anti-tumor immune response with immunomodulators, or to help the body's immune system recognize tumor cells. Passive immunity is an artificial method that directly injects immune substances (such as antitoxins, gamma globulin, lymphocytes, etc.) into the body to obtain certain biological products to inhibit or kill tumor tissues, but it has the limitation of killing a certain

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type of tumor cells against a single tumor antigen and the penetration problem of antibody drugs [37]. At present, domestic and foreign studies on glioma immunotherapy include vaccine therapy, immune checkpoint inhibitors, chimeric antigen receptor T cell therapy, oncolytic virus therapy, cytotoxic T lymphocyte-associated antigen 4, programmed death receptor-1 / programmed death receptor-ligand 1 inhibitors, etc. Dendritic cell vaccine therapy is the focus of research, and its key antigen presenting cells participate in the uptake and presentation of tumor-related antigens and initiate the tumor immune response mediated by T cells. Preliminary results of many phase I and II clinical studies have shown that dendritic cell vaccines sensitized by autologous tumor lysate products can effectively inhibit the progression of glioma and prolong the survival of patients with maximum safe tumor resection [38]. Due to the remarkable results of initial clinical trials, many phase III clinical trials are currently underway.

6.2.3. Tumor electric field therapy

Tumor electric field therapy is a kind of low-intensity, medium-frequency alternating electric field interferes with the activity of tumor cells to achieve the purpose of anti-tumor in a local area, and this effect does not affect the cells in the quiescent stage. The mechanism of tumor electric field therapy is mainly to inhibit mitosis, induce cell apoptosis, enhance immune response, inhibit tumor cell metastasis, and affect the permeability of cell membrane and the integrity of blood-brain barrier [39]. Studies have shown that tumor electric field therapy can affect the permeability of cell membrane and the integrity of the blood-brain barrier, and can promote the arrival of chemotherapy drugs to tumor cells to play a role, significantly improving the prognosis compared with single chemotherapy drug treatment, while not affecting the quality of life [40-42]. Compared with radiotherapy alone, although electric field therapy combined with radiotherapy can increase the degree of local skin damage, it does not increase the toxic reaction of radiotherapy [43]. An EF-32 Phase IV global clinical trial of combined electric field therapy and temozolomide maintenance therapy combined with electric field therapy during postoperative radiotherapy is underway, with a primary focus on OS in patients with glioma, and is expected to be completed in August 2024.

7. Summary

This article summarizes the research progress in the field of brain glioma. The treatment of glioma is still a worldwide problem. Considering the heterogeneity, genomic complexity and multiple signaling pathways of the tumor, the ideal treatment measures should be perfect intraoperative treatment and comprehensive postoperative treatment, and no single treatment regimen can completely cure glioma [44]. It is very necessary to explore the development mechanism of glioma and new treatment strategies, which is of great significance in improving the prognosis and prolonging the survival time of glioma in the future.

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