Review article

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Age-related aspects of glioma: current understanding. Literature review

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The updated 2021 WHO Classification of Central Nervous System (CNS) Tumors introduces, for the first time, an age-based approach to glioma classification, leveraging advances in molecular biology and epigenetics of CNS tumors. This classification groups gliomas within the category "Gliomas, glioneuronal tumors, and neuronal tumors," distinguishing between adult-type and pediatric-type diffuse gliomas, corresponding to low-grade and high-grade malignancies (LGG and HGG), highlighting the fundamental role of age in gliomagenesis. A review of current literature deepens the understanding of age-related characteristics, differences, and patterns in gliomagenesis across age groups, which is essential for effective diagnosis and treatment.

Pediatric-type and adult-type low-grade gliomas (pLGG and aLGG) differ in location, biological behavior, and molecular-genetic profiles. Inherited syndromes (e.g., NF-1, TSC) associated with glioma development are linked to specific LGG subtypes occurring in childhood, adolescence, and adulthood. Moreover, pLGG differs from aLGG in its potential for malignant transformation and spontaneous regression, as well as in mutations affecting the MAPK (mitogen-activated protein kinase) pathway.

While pediatric-type and adult-type high-grade gliomas (pHGG and aHGG) share histological features, they differ in location, biological behavior, molecular-genetic profiles, and prognosis. A major distinction between aHGG and pHGG lies in mutations such as *IDH 1/2*, *EGFR* gene expression, *TERT* mutations, chromosome alterations (+7/-10), and *TP53* mutations, all contributing to a poorer prognosis in HGG gliomas. Additionally, changes in histone proteins H3.3 or 3.1 (H3.3 K27 and H3 G34) in pHGG, as opposed to aHGG, carry diagnostic and prognostic significance.

An analysis of data on glioma epidemiology, risk factors, and characteristic molecular-genetic features considering age is provided. The next publication will cover certain clinical aspects of this issue.

Keywords: *glioma; age-related differences in gliomas; adult-type and pediatric-type gliomas; low-grade and high-grade gliomas*

Introduction

The diagnosis and treatment of gliomas—the most common tumors of the central nervous system (CNS)—represent a significant healthcare burden worldwide. In the United States alone, approximately 18,500 cases of malignant gliomas are diagnosed annually. Medical care for one patient, including surgical intervention and radiation therapy, costs between $50,600 and $92,700 USD per year [1]. Adding chemotherapy (temozolomide and bevacizumab) for glioblastoma (GBM) treatment further increases expenses, costing €20,587.53 and €5,581.49 per year per patient, respectively, for caregivers providing support [2]. Identifying causes and risk factors for glioma development enables the timely implementation of preventive measures to reduce incidence across different population groups—an approach that is more cost-effective than the expenses associated with treatment, rehabilitation, and patient care.

The literature increasingly emphasizes the relevance of age in gliomagenesis [3]. Glioma incidence rises significantly with age, particularly after 65 years [3-5]. *Low-grade gliomas* (LGG) are more common in children, while *high-grade gliomas* (HGG) are typically observed in adults.

In 2021, the WHO Classification of tumors of the central nervous system was updated. The primary distinction in this edition was the introduction of an age-based approach to glioma characterization [6-8]. This marks the sixth version of the international standard for CNS tumor classification, with previous editions published by WHO in 1979, 1993, 2000, 2007, and 2016.

Building on the 2016 WHO CNS Tumor Classification [8] and recommendations from the *Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy* (cIMPACT-NOW) [9], a number of significant changes and additions have been made to the WHO Classification of brain and spinal cord tumors (2021) [6, 10]. Gliomas are now classified within the family "Gliomas, glioneuronal tumors, and neuronal tumors," with the following types: *circumscribed astrocytic gliomas*, *adult-type diffuse gliomas*, *pediatric-type diffuse low-grade gliomas* (pLGG), and *pediatric-type diffuse high-grade gliomas* (pHGG). The division of diffuse gliomas into adult- and pediatric-type categories underscores the important role of age, which may substantially influence gliomagenesis, biological behavior, molecular-genetic profiles, and prognosis, and should be considered in the diagnosis and treatment of gliomas across all age groups [6, 10-13].

Epidemiology of gliomas considering age and other factors

Recent large-scale clinico-epidemiological studies conducted in recent years indicate that the incidence, prevalence, and mortality rates of gliomas depend on factors such as age, gender, race, geographic region, and other variables [14].

Gliomas account for approximately 24.5% of all primary brain tumors and about 81% of all malignant central nervous system (CNS) tumors in adults [15]. About 62% of gliomas are located in the supratentorial region: 27.0% in the frontal lobe, 20.2% in the temporal lobe, 11.6% in the parietal lobe, and 2.8% in the occipital lobe. Tumor location influences the surgical approach. Gliomas may also be found in the brainstem (4.3%), cerebellum (2.8%), and other CNS areas (around 20.0%) [16]. The most common glioma is glioblastoma (GBM), accounting for 14.2% of all CNS tumors, 50.1% of all malignant CNS tumors, and approximately 45% of all gliomas, with a higher incidence among men (incidence rate ratio of 1.57) [17–19]. GBM is the most aggressive CNS tumor with a poor prognosis; the five-year relative *overall survival* (OS) rate is less than 5% [18].

Current reports, such as those from the *Central Brain Tumor Registry of the United States* (CBTRUS), provide data on glioma incidence, prevalence, and mortality derived from registries that classify glioma cases according to the 2007 and 2016 WHO CNS classifications. Thus, the tumor nomenclature, particularly for gliomas, differs from that in the 2021 WHO Classification of tumors of the brain and spinal cord [8,13,20]. The types of gliomas according to the WHO Classification of Brain and Spinal Cord Tumours (2021) are presented in a table ***(Table 1)***, facilitating a better understanding and assessment of studies conducted before the updated classification was adopted.

According to extensive epidemiological research by Q.T. Ostrom et al. [14, 16–19], astrocytic tumors, specifically GBM, represent 77.5% of all gliomas. Among malignant gliomas, other notable types include diffuse astrocytoma (7.3% of all gliomas), anaplastic astrocytoma – 6.8%, oligodendroglioma – 3.5%, anaplastic oligodendroglioma – 1,7%, pilocytic astrocytoma – 5.0%, and unspecified gliomas (NOS) - 7.9%.

The highest incidence of GBM among adults is 3.23 per 100,000 population, while rates for diffuse and anaplastic astrocytoma are 0.46 and 0.42 per 100,000, respectively. For oligodendroglioma and anaplastic oligodendroglioma, the rates are 0.23 and 0.11 per 100,000 [16,17,19]. The peak ages for diffuse astrocytoma and oligodendroglioma are at mean age of 46 and 43 years, respectively, while anaplastic astrocytoma and oligodendroglioma peak at ages 53 and 49. GBM is a prevalent tumor among adults, particularly the elderly (average age of 65), whereas GBM is rare in children [15].

In children, gliomas account for 45% of all malignant CNS tumors [21, 22]. Among pediatric gliomas, midline glioma ranks first, representing 31.1% of all childhood gliomas, while pilocytic astrocytoma accounts for 18.3%, diffuse and anaplastic astrocytoma for 5.3%, and glioblastoma multiforme (GBM) for 2%.

In the age group 0–19 years, the incidence of diffuse midline glioma is 0.31 per 100,000 population, while diffuse astrocytoma and GBM have incidences of 0.23 and 0.17 per 100,000 population, respectively [15]. Anaplastic astrocytoma, oligodendroglioma, and anaplastic oligodendroglioma are rare in this age group, with incidences of 0.09, 0.04, and 0.01 per 100,000 population, respectively.

The highest incidence rate of gliomas is registered in males (5.51 and 3.65 per 100,000 population, respectively), although females have a higher incidence of diffuse midline glioma—0.324 and 0.288 per 100,000 population, respectively [14, 15].

In the United States, malignant CNS tumors in children (aged 0–14 years) rank second in pediatric mortality rates, and in 2016 they were the leading cause of death among children [23,24]. The incidence rate of malignant CNS tumors in the pediatric population from 1998 to 2013 remained relatively stable, with an *annual percent change* (APC) of 0.16% per year (95% confidence interval (CI) 0.21–0.53). An increase in incidence was recorded for certain tumor types, including gliomas (APC 0.77% per year (95% CI 0.29–1.26)) and pilocytic astrocytoma (APC 0.89% per year (95% CI 0.21–0.53)), while a decrease in LGG gliomas (12.9% of all gliomas; APC -2.85 (95% CI 1.46–4.23)) and an increase in HGG gliomas (21.3% of all gliomas; APC -1.25 (95% CI 0.68–1.83)) and other gliomas (65.8% of all gliomas; APC -1.55 (95% CI 0.18–2.95)) were observed [15, 23]. These results are consistent with those reported by R. McKean-Cowdin et al. [25], obtained from 1973–2009, indicating that factors such as availability of specialized neurosurgical care, the quality of glioma diagnostics, and the accuracy and completeness of registry data on glioma cases influence these findings.

Epidemiological studies suggest regional variability in glioma incidence. It is hypothesized that the aging populations observed in recent decades in Europe and North America may partially explain the high glioma incidence, especially GBM, which increased on average by 2.9% per year from 1978 to 1992 [26–29]. The incidence of malignant gliomas increased from 1998 to

2008 among the elderly, while the CBTRUS registry data indicate relative stability among those aged ≥40 years from 2000 to 2016 [16, 20, 30].

Brainstem gliomas (BSG) represent a type of malignant CNS tumor that is rare in adults (1–2% of all gliomas) but common in children (20% of all gliomas) and has a poorer prognosis in children than in adults [31, 32]. The 5-year OS rates are 94.7% for pilocytic astrocytoma and 6.8% for GBM [14, 15, 26].

Table 1. Classification of gliomas according to the 2021 WHO Classification of tumors of the Brain and Spinal Cord

Type of glioma	WHO CNS Grade	Characteristic molecular and genetic alterations *
Circumscribed astrocytic gliomas		
Pilocytic astrocytoma	1	*KIAA1549-BRAF, BRAF, NF1*
High-grade astrocytoma with pi14locytic features	NS‡	*BRAF, NF1, ATRX, CDKN2A/B (methylome)*
Pleomorphic xanthoastrocytoma	2, 3	*BRAF, CDKN2A/B*
Subependymal giant cell astrocytoma	1	*TSC1, TSC2*
Chordoid glioma	2	*PRKCA*
Astroblastoma, MN1-altered	NS	*MN1*
Adult-type diffuse gliomas (aDG)		
Astrocytoma, IDH-mutant	2, 3, 4	*IDH1, IDH2, ATRX, TP53, CDKN2A/B*
Oligodendroglioma, IDH-mutant and 1p/19q codeleted	2, 3	*IDH1, IDH2, 1p/19q, TERT promoter, CIC, FUBP1, NOTCH1*
Glioblastoma, IDH wild-type	4	*IDH-wildtype, TERT promoter chromosomes 7/10, EGFR*
Pediatric low-grade diffuse gliomas (pLGG)		
Diffuse astrocytoma, MYB - or MYBL1 altered	1	*MYB, MYBL1*
Angiocentric glioma	1	*MYB*
Polymorphous low-grade neuroepithelial tumor of young	NS*	*BRAF, FGFR family*
Diffuse low-grade glioma, MAPK pathway-altered		*FGFR1, BRAF*
Pediatric high-grade diffuse gliomas (pHGG)		
Diffuse midline glioma, H3 K27-altered	4	*H3 K27, TP53 , ACVR1 , PDGFRA, EGFR, EZHIP*
Diffuse hemispheric glioma, H3 G34-mutant	4	*H3 G34, TP53 , ATRX*
Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wild-type	4	*IDH- wild-type, H3- wild-type, PDGFRA, MYCN, EGFR (methylome)*
Infant-type hemispheric glioma	NS‡	*NTRK family, ALK, ROS, MET*

Notes: * - molecular and genetic changes, which are often common, are listed first. "methylome" is specified only for gliomas where it is recommended for diagnostic purposes. NS – not specified; NS * – not specified for LGG; not specified NS ‡ – not specified for HGG. Genes: BRAF – proto-oncogene B-Raf, serine/threonine kinase; KIAA1549-BRAF – gene fusion;NF1 – neurofibromin 1; ATRX – alpha-thalassemia/mental retardation syndrome, linked to the X chromosome; CDKN2A/B – cyclin-dependent kinase inhibitor; TSC1, TSC2 – tuberous sclerosis proteins 1 and 2; PRKCA – protein kinase C alpha; MN1 – proto-oncogene, transcription regulator; IDH – isocitrate dehydrogenase; TERT – telomerase reverse transcriptase; CIC – transcriptional repressor HMG-box; FUBP1 – oncogene; NOTCH1 – single-pass transmembrane receptor; NTRK – neurotrophic tyrosine receptor kinase gene family; EGFR – epidermal growth factor receptor; MYB – proto-oncogene, transcription factor; MYBL1 – MYB-like proto-oncogene 1; FGFR – fibroblast growth factor receptor; H3 – histones H3 K27 and H3 G34; ACVR1 – activin type I receptor; PDGFRA – platelet-derived growth factor receptor alpha; EZHIP – EZH inhibitory protein; TP53 – transcription factor p53; MYCN – proto-oncogene, transcription factor bHLH; ALK – anaplastic lymphoma receptor tyrosine kinase; ROS – proto-oncogene receptor tyrosine kinase; MET – proto-oncogene, receptor tyrosine kinase.

Risk factors (determinants) of gliomas

The risk factors, or determinants, for the development of gliomas are not yet fully defined, and data from the literature are contradictory. However, understanding these factors is useful for the prevention and early diagnosis of gliomas. Despite numerous publications on identifying glioma risk factors, only a few are considered proven, including genetic factors (hereditary disorders and syndromes) and ionizing radiation [14, 33-36].

Genetic (hereditary) disorders and syndromes. It is known that most gliomas occur without a burdensome family history, with only 5% of cases having such a history, and in 1% of cases, established hereditary disorders/syndromes are present in patients with glioma [14, 33]. Studies on the associations between genetic disorders and the risk of CNS tumors indicate that certain hereditary disorders are closely linked to glioma risk [14]. The most significant hereditary disorders and syndromes, their modes of inheritance, and chromosomal and genetic changes associated with glioma risk are presented in ***Table 2***. Among hereditary disorders, particular attention is given to Li-Fraumeni syndrome, caused by alterations in the *TP53* gene, which encodes the tumor suppressor protein P53; Turcot's syndrome type 1, which combines primary brain tumors with colorectal cancer; neurofibromatosis type 1; and tuberous sclerosis. These conditions are associated with the highest risk [14, 33-35].

Aging is associated with telomere shortening, while the risk of gliomas is linked to telomere lengthening [33, 36]. Shortened telomeres suppress cell proliferative activity, potentially inhibiting tumor development. In contrast, telomere lengthening is associated with high proliferative activity, which may increase the likelihood of somatic mutations, and thus, the risk of brain tumors, including gliomas (odds ratio (OR) = 1.16, 95% CI 1.02–1.31) [36]. The mean telomere length in glioma patients is 31 bp (5.7%) longer than in controls, and with each increase in telomere length septile, the glioma risk rises (OR = 1.12, 95% CI 0.90–1.62). It is known that *single nucleotide polymorphisms* (SNPs) in *TERC* and *TERT* alleles, which are associated with telomere length, may play a central role in gliomagenesis [33, 34, 36].

Ionizing Radiation is one of the most thoroughly studied and proven risk factors for gliomas in children, adolescents, and adults [34]. The International agency for research on cancer (IARC) classifies ionizing radiation as a Group 1 carcinogen [37]. In IARC's publication, studies involving large cohorts of children and adolescents (up to age 19) who received therapeutic radiation for medical reasons showed a twofold increase in glioma risk within nine years post-treatment. Glioma risk was found to have a linear dose-response relationship, with the highest risk per unit of absorbed dose (1 Gy) observed in children under five.

Non-Ionizing Radiation (NIR), which includes microwave radiation in the radiofrequency range and extremely low-frequency magnetic fields, has also been studied. The IARC has classified radiation within the 30–300 GHz range as a Group 2B possible human carcinogen [38]. Concerns about NIR's role in glioma development have risen in recent decades due to the widespread use of mobile (cellular) communication devices [14, 39-42]. Mobile phones are a common source of NIR, with 97-99% of absorbed energy impacting the brain hemispheres, and 50-60% affecting the temporal lobe and cerebellum. Despite numerous large clinical and epidemiological studies (INTERPHONE, CERENAT, COSMOS) conducted in recent decades, their results on glioma risk from NIR exposure remain inconclusive [39-44]. This issue is the subject of ongoing debate in the scientific community and is discussed in government and international institutions, especially with the active adoption of new 5G technologies [45, 46].

Table 2. Hereditary disorders and syndromes associated with glioma (adapted from [14]

Syndrome/disorder	Inheritance type	Gene alterations (chromosomes)
Li-Fraumeni syndrome (LFS)	Dominant	*TP53 (17p13.1)*
Turcot's syndrome Type 1 (ST1)	Autosomal recessive	*MLH1, PMS2*
Familial adenomatous polyposis, Turcot's syndrome Type 2 (ST2)	Dominant	*APC, MMR (5q21)*
Neurofibromatosis 1 (NF1)	Dominant	*NF1 (17q11.2)*
Tuberous sclerosis (TSC)	Dominant	*TSC1,TSC2 (9q34.14,16p13.3)*
Rubinstein-Taybi syndrome	Dominant	*CREBBP, EP30 (16p13.3; 22q13.2)*
Ollier disease	Acquired postzygotic mosaicism, dominant with reduced penetrance	*IDH1/IDH2 (2q33,3/15q26,1)*
Lynch syndrome	Dominant	*MSH2, MLH1, MSH6, PMS2*
Mismatch repair deficiency syndrome	Recessive	*MSH2, MLH1, MSH6, PMS2*
Retinoblastoma syndrome	Dominant	*RB1 (13q14)*
Melanoma-neural system tumor syndrome	Dominant	*CDKN2A (9p21.3)*
Ataxia-telangiectasia	Autosomal recessive	*ATM (11q22.3)*

Biological factors, including infectious disease agents such as Herpes Simplex Virus types 1 and 2 (HSV), Human Papillomavirus (HPV), Varicella-Zoster Virus (VZV), Cytomegalovirus (CMV), Epstein-Barr Virus (EBV), and others, are of interest to researchers not only for assessing glioma risk but also for exploring immunotherapy options through antiviral vaccines [47-50].

For many years, CMV infection was thought to be associated with gliomagenesis [47]. A meta-analysis [49] found that previous CMV infection increased the incidence of glioma (OR 3.95, 95% CI 1.7–5.3). However, the results of other studies have shown that individuals with a previous VZV-associated infection had a significantly reduced risk of LGG gliomas (HR 0.85, 95% CI 0.76-0.96) [51], and the risk of GBM was 30% lower compared with control group. This may be because VZV can trigger immune response reactions aimed at viral infections, which cross-react with GBM cell membrane proteins, thus generating an immune response against tumor cells [18]. The decrease in anti-VZV IgG levels in GBM compared with control group supports its protective role in gliomagenesis. A prospective study of the association between infections caused by HS, VZV, CMV, and EBV viruses and glioma risk indicate that EBV infection is associated with a lower risk of glioma development (OR = 0.57, 95% CI 0.38–0.85) [52]. There is no evidence of an increased risk of glioma in the presence of HPV infection [52, 53]. Consequently, there are no definitive conclusions about the causal relationship between viral infections and the risk of glioma development. The study of this issue is relevant because of the likelihood of distant consequences of infection due to the *SARS-COV-2* virus that caused the outbreak of the 2019 coronavirus disease pandemic (COVID-19) [54]. Upon entry into the body by respiratory route, *SARS-CoV-2* virus interacts with target cells and initiates a complex cascade of immune response reactions. At the same time, the tropism of SARS-CoV-2 virus to receptors on the surface of certain cell types can cause a high risk of severe course of the disease and its long-term consequences [55, 56].

It is known that the *SARS-CoV-2* S-glycoprotein can interact with receptor proteins on the surface of target cells, specifically with angiotensin-converting enzyme 2 (ACE2), which facilitates viral entry into cells [57]. This interaction plays a key role in the pathogenesis of COVID-19. The expression of ACE2 on the surface of glial cells and neurons characterizes them as potential targets for *SARS-CoV-2* [56]. Glioma cells express epidermal growth factor (EGFR), vascular endothelial growth factor (VEGFR), and hepatocyte growth factor (HGFR/c-MET) receptors, which are associated with tumor development and invasion [58]. ACE2 expression on cell surfaces enables the initiation of signaling pathways that play a central role in tumorigenesis. Recent studies have shown that the S glycoprotein of *SARS-CoV-2* has high affinity for the receptor proteins EGFR, VEGFR, and c-MET, which may indicate a potential role of COVID-19 in the development of gliomas [59, 60].

Age-related differences in low-grade gliomas

Gliomas represent about one-third of CNS tumors. In children and adolescents, two-thirds of gliomas are categorized as pediatric low-grade gliomas (pLGG). In adults and the elderly, aLGG gliomas are rare (15–20% of all gliomas) [63–65].

The research results by L. Greuter et al. [65] indicate that pLGG and aLGG gliomas have several age-related differences in terms of localization, malignancy grade, molecular-genetic status, potential for malignant transformation, association with hereditary pathology, prognosis, and so on, which are relevant for diagnosis, treatment, and prognosis ***(Table 3)***.

In children and adolescents, most gliomas are classified as diffuse Grade 1 gliomas according to the WHO Classification of Tumors of the Central Nervous System (2021), while in adults, most LGG gliomas are Grade 2 [66]. Most pLGG gliomas are located in the cerebellum, whereas in adults, they are typically found in the supratentorial region of the brain. pLGG gliomas are characterized by a more favorable prognosis compared to aLGG gliomas [65]. The majority of aLGG gliomas can undergo malignant transformation into HGG gliomas, whereas malignant transformation in pLGG gliomas is rare [67–69]. Approximately 6% of pLGG gliomas have the ability to spread to other areas of the CNS, while in adults, this capability is observed only in HGG gliomas [70, 71].

Hereditary syndromes, as noted above ***(see Table 2)***, are associated with the risk of LGG glioma development in both children and adults [14,15,35,65,72]. Specifically, NF-1 syndrome is associated with a risk of optic pathway glioma in 6% of patients aged 3–4 years and is characterized by a relatively benign course and favorable prognosis [73–75]. In 1% of NF-1 patients, brainstem glioma has been reported, often accompanied by hydrocephalus [76]. TSC is a multisystem autosomal dominant hamartoma syndrome caused by mutations in the TSC1 or TSC2 genes, which enhance the regulation of cell cycle signaling pathways and lead to the development of certain types of gliomas, primarily of astrocytic origin, with only a few cases reported in the literature [77]. These tumors mostly occur in children and young adults and are not found in adults.

Surgical intervention assessment indicates that *gross total resection* (GTR) of glioma correlates with increased overall survival (OS) and *progression-free survival* (PFS) in both children and adults. It is reported that *subtotal resection* (STR) with minimal residual tumor shows similar outcomes to GTR, although data on this are conflicting [65, 78].

Glioma localization is a factor that determines an unfavorable prognosis for pLGG located in the brainstem and for *optic pathway gliomas* (OPG), though not for OPG in patients with NF-1. Prognostic factors include STR, young age, and tumor location, particularly within the brainstem or optic pathway [14, 65, 79].

In adults with LGG glioma, the likelihood of a favorable GTR outcome increases if the tumor is detected without specific symptoms and at an early stage, as opposed to cases with pronounced glioma symptoms. According to AJ Gogos et al. [78], the average growth rate of such "incidental gliomas" is 3.9 cm^3/year. Gross total resection (GTR) is achieved in 57% of cases compared to 24% in patients with characteristic glioma symptoms. In cases with STR, the residual tumor volume averaged 2.9 cm^3, impacting glioma prognosis (OS for patients with

"incidental gliomas" is around 14.6 years) [78]. For aLGG, early GTR after tumor detection increases the likelihood of a favorable prognosis compared to delayed tumor resection, indicating the importance of GTR as a primary treatment method for both aLGG and pLGG gliomas. However, GTR is found to be more effective for pLGG gliomas than aLGG gliomas, likely due to differences in their morphology and biological behavior.

Molecular-genetic, diagnostic, and prognostic factors. Recent research on the molecular-genetic profile of pLGG gliomas has revealed changes in the MAPK/ERK pathway (*mitogen-activated protein kinase/extracellular signal-regulated kinase*) caused by BRAF gene mutations or fusions, which are not characteristic of aLGG gliomas [80–83]. Alterations in the MAPK pathway are also typical for NF-1 syndrome, which predisposes to pLGG [83]. It is reported that 84% of pLGG gliomas are characterized by a mutation in the *BRAF* gene encoding the B-Raf protein (*B-Raf proto-oncogene, serine/threonine kinase*). The *KIAA1549-BRAF* fusion is common in pilocytic astrocytoma (35%), while *BRAFV600E* mutations and NF-1 are observed in only 17% of pLGG cases [81]. Molecular-genetic profiling of gliomas at the diagnostic stage is crucial for treatment and prognosis [11,13,82,83]. The *KIAA1549-BRAF* alteration is characteristic of cerebellar pLGG gliomas and is associated with significantly higher 5-year progression-free survival (PFS) compared to pLGG with a *BRAFV600E* mutation (69% vs. 52%) and 10-year overall survival (OS) (97% vs. 89%) [81]. Most pLGG gliomas typically exhibit at least one mutation impacting the MAPK pathway.

Age-specific features of malignant transformation (MT) in LGG are observed in only 2.9–6.7% of pLGG cases [65,85]. In children, MT is often associated with previous chemotherapy and/or radiotherapy. In contrast, MT occurs more frequently in adults (13–86% of all aLGG gliomas), especially in pregnant women, which may be associated with hemodynamic and metabolic changes due to elevated levels of progesterone and insulin-like growth factor-1 (IGF-1), which particularly correlates with astrocytoma development [85,86].

Spontaneous regression of pLGG has been documented as a phenomenon in certain types of pLGG gliomas, particularly in rare cases of cerebellar gliomas. Regression has been recorded in 30% of cerebellar pLGG gliomas on average 11.9 months after STR. Other studies report spontaneous regression in 32.5–48% of cerebellar pLGG glioma cases [65].

Thus, pLGG and aLGG gliomas differ in anatomical localization, biological behavior, and molecular-genetic profiles, which is essential for the diagnosis, treatment, and prognosis of LGG gliomas in children and adults. Hereditary syndromes, such as NF-1 or TSC, are associated with specific types of pLGG gliomas that arise in childhood.

Table 3. Differences between pediatric and adult low-grade gliomas (adapted from [65]

Indicator	pLGG	aLGG
Localization	Supratentorial (30%) Infratentorial (30%)	Supratentorial (80%)
Histological grading	Grade 1* (74%) Grade 2* (26%) Pilocytic astrocytoma (65%)	Grade 1* (10–15%) Grade 2* (85–90%) Diffuse glioma LGG (60%)
Associated hereditary disorders	NF-1 (TSC)	-
Molecular alterations	*BRAF600 (17%)*	*IDH-mutant (70%)*
Treatment	GTR increases OS	GTR increases OS
Malignant transformation	Rare (2.9–6.7%), may increase post-CT or RT	Frequent (86%)
10-Year OS, %	>90	~60
Prognosis	OPG and brainstem glioma – unfavorable; OPG with NF-1 – favorable; GTR – favorable; young age – unfavorable	Gliomas (typical sites) – unfavorable; GTR – favorable; Diffuse Grade 1 gliomas* – unfavorable; age <40 – favorable

*Note.** – according to the WHO Classification of Tumors of the brain and spinal cord tumors (2021); NF-1 – neurofibromatosis type 1; TSC – tuberous sclerosis; BRAF600 – B-Raf proto-oncogene serine/threonine kinase; IDH – isocitrate dehydrogenase gene; OPG – optic pathway glioma; GTR – gross total resection; CT – chemotherapy; RT – radiotherapy.

Age-related differences in high-grade gliomas

According to the WHO Classification of Tumors of the Central Nervous System (2021), HGG gliomas include circumscribed WHO CNS grade 3 gliomas, as well as diffuse adult-type WHO CNS Grade 3 and 4 gliomas (*IDH*-mutant astrocytoma, *IDH*-mutant oligodendroglioma with 1p/19q codeletion, *IDH*-wild-type glioblastoma) and all pediatric-type diffuse HGG gliomas ***(Table 1)***.

Age-related differences in glioma localization. In adults, *IDH*-mutant astrocytoma can occur in any part of the brain, most commonly in the subtentorial region and frontal lobe. The average age of patients with this type of glioma is 30–40 years, rarely over 55 years [87,88]. The average age for patients with WHO CNS Grade 4 *IDH*-mutant astrocytoma is 42 years, while for Grade 2-3 it is 38 years. *IDH*-mutant oligodendroglioma with 1p/19q codeletion is most often observed in patients aged 40–50 years and is very rarely seen in children. Most tumors are located in the frontal lobe, less frequently in the temporal or parietal lobes, and very rarely in the brainstem [88]. *IDH*-wild-type GBM, which is also characterized by EGFR amplification and/or *telomerase reverse transcriptase* (TERT) promoter mutation and/or chromosomal alterations (+7/–10), accounts for half of all malignant brain tumors in adults and elderly individuals, with 10,000 new cases reported annually [89]. GBM develops between 18 and 89 years, most frequently (58%) between 50 and 69 years [88, 90, 91]. Comorbidities in older individuals result in a poorer prognosis for glioma compared to younger patients, due to limitations in standard glioma treatments caused by concurrent diseases.

In children and adolescents, diffuse HGG gliomas account for 3 to 15% of primary CNS tumors, with pHGG patient OS averaging 10–73 months [89,92]. Diffuse midline glioma, H3K27-altered, develops in individuals aged 2 to 65 years, with a median age of 11–14 years. Its pathognomonic feature is localization in the brainstem, thalamus, hypothalamus, as well as the cerebellum and spinal cord. The median age for brainstem glioma is 7 years, for thalamic glioma 24 years, and for spinal cord glioma 25 years. The prognosis for this glioma is poor, with an OS of 1 year [92].

Diffuse hemispheric glioma, H3G34-mutant, is most common between ages 15 and 19, and according to some studies, between 18 and 26 years. The prognosis for this glioma is generally poor (OS from 12 to 36 months) [92, 93].

H3-wild-type and *IDH-wild-type pHGG* gliomas are usually located in the brain hemispheres and rarely in other brain regions. These gliomas are often detected in early childhood but can also occur in adolescence and early adulthood. The prognosis for such gliomas is unfavorable (OS of 22 months) [90, 92, 93].

Molecular-genetic, diagnostic, and prognostic factors in aHGG and pHGG gliomas. Among HGG gliomas, diffuse gliomas are the most common. Although there are practically no histological differences between diffuse aHGG and pHGG gliomas, they differ in biological behavior, molecular-genetic characteristics, treatment response, and prognosis [92, 94, 95]. The defining differences between diffuse aHGG and pHGG gliomas, as reflected in the WHO Classification of CNS Tumors (2021), are molecular-genetic characteristics ***(Table 4)***.

Table 4. Age-related differences in the molecular-genetic profile of diffuse high-grade gliomas [92]

Molecular and genetic alterations	pHGG	aHGG	Implications
IDH1 Mutation	In 16.3–35.0% of cases in children over 14 years old	~50% of primary HGG gliomas	Astrocytoma, IDH-mutant
EGFR Expression	In approximately 80% of cases	Amplification and overexpression in 27–60% of cases	Grade 4 glioma*
TERT Promoter mutations	Rarely	In 40–70% of cases	Grade 4 glioma*
Chromosomal alterations +7/–10	NS	У 50–70% випадків	Grade 4 glioma*
TP53 Mutation	In 33–58% of pediatric cases	In 30–60% of GBM cases	p53 – tumor suppressor
Loss or Mutation of PTEN	In 0–20% of cases	In 27–60% of cases	Alterations in the PI3K/AKT/mTOR signaling pathway
H3 K27- mutant	In 60–80% of cases	NS	Pediatric diffuse midline glioma, Grade 4*
H3 G34- mutant	In approximately 20% of cases	NS	Pediatric diffuse hemispheric glioma, Grade 4*

Note. * Based on the WHO Classification of Tumors of the Central Nervous System (2021); EGFR – epidermal growth factor receptor gene; TERT – telomerase reverse transcriptase promoter gene; TP53 – p53 tumor suppressor gene; PTEN – phosphatase and tensin homolog gene; IDH – isocitrate dehydrogenase gene; H3 K27 and H3 G34 – histone H3 proteins; Not specified – NS.

The key difference between aHGG and pHGG is the *IDH 1/2* gene mutations, which have diagnostic and prognostic significance, since *IDH* mutation in HGG gliomas determines a significantly better prognosis for adult and paediatric gliomas compared with *IDH*-wild-type gliomas [7,13,93,96]. Astrocytoma, *IDH*-mutant with homozygous deletion of *CDK2A/B*, is classified as a WHO CNS Grade 4 glioma with a poor prognosis ***(see Table 1)***. For gliomas, *IDH*-wild type, the presence of mutations such as *EGFR* amplification, *TERT* promoter mutations and chromosome +7/-10 alterations are a factor of unfavourable prognosis for patients ***(see Table 4)***.

EGFR amplification affects the tyrosine kinase receptor involved in cell proliferation and differentiation, as well as malignant growth processes. It is observed in 60% of GBM cases in adults, while it is rare in pHGG diffuse gliomas [92, 97, 98, 99].

Among other genes that cause age-related differences in gliomas, the *phosphatase and tensin homologue* (*PTEN*) suppressor gene, which is able to inhibit tumour invasion and blood vessel formation, occupies an important place. Its mutations are frequently reported in aHGG and rarely in pHGG. The *TP53* gene is also a tumour suppressor gene with alterations in the majority of adult GBM cases [96, 99].

In the case of pHGG gliomas, in contrast to aHGG gliomas, alterations in histone proteins, particularly H3, are important for diagnosis and prognosis. Thus, diffuse medial glioma of pHGG is characterised by K27M mutation in histones H3.3 or H3.1. Diffuse hemispheric gliomas of pHGG are characterised by the presence of H3 G34R or H3 G34V mutation. pHGG gliomas with histone mutations usually have a poor prognosis and significantly lower OS compared to diffuse H3-wild-type and *IDH*-wild-type gliomas [98, 100-101]. In diffuse pHGG gliomas, TP53 mutations are often found together with H3 mutations. Therefore, histone mutation status may play a key role in gliomagenesis, especially in children, adolescents, and young adults, which is important for diagnosis, selection of adequate treatment methods, and prognosis of diffuse gliomas of pHGG.

Amplification of the platelet-derived growth factor receptor A (*PDGFRA*) gene in diffuse H3G34-mutant hemispheric gliomas is associated with an unfavorable prognosis, while O6-methylguanine DNA methyltransferase MGMT-methylation is associated with a more favorable prognosis, including increased survival. Specific molecular-genetic alterations in H3 wild-type and *IDH* wild-type diffuse pHGG gliomas also significantly impact prognosis. For example, the OS of patients with gliomas showing *MYCN* amplification averages 14 months, with *PDGFRA* amplification – 21 months, and with *TERT* or *EGFR* mutation 44 months [92, 96].

Conclusions

1. In light of recent research findings, the 2016 WHO Classification of Tumors of the Central Nervous System has been revised, and in 2021, an updated version was approved. According to this new classification, gliomas are grouped within the "Gliomas, glioneuronal, and neuronal tumors" family, divided into the following types: circumscribed astrocytic gliomas, adult-type diffuse gliomas, pediatric-type low-grade diffuse gliomas, and pediatric-type high-grade diffuse gliomas. The distinction of gliomas into adult and pediatric types, which share similar histological characteristics but differ substantially in biological behavior, molecular-genetic profile, and prognosis, emphasizes the significant role of age in influencing gliomagenesis. This must be considered in both diagnosis and treatment of gliomas.

2. Analysis of the current literature on the theoretical and applied aspects of gliomas—the most common CNS tumor types—provides an opportunity to deepen understanding of the age-related features, differences, and patterns of gliomagenesis across all age groups affected by gliomas. Additionally, this analysis highlights distinct and shared characteristics of gliomas in adults and children, which can enhance prevention measures, improve diagnostics, treatment, and prognostication for patients of various ages.

3. Pediatric- and adult-type low-grade gliomas differ in anatomical location, biological behavior, and molecular-genetic profile, which has crucial implications for diagnosis, treatment, and prognosis. Hereditary syndromes associated with glioma development (NF-1, TSC) are linked to specific low-grade glioma types that can arise in childhood, adolescence, and adulthood. In contrast to aLGG, pLGG is characterized by the presence of at least one mutation affecting the MAPK pathway. Furthermore, pLGGs differ from aLGGs in their potential for malignant transformation and spontaneous regression.

4. Pediatric- and adult-type high-grade gliomas share similar histological characteristics but differ in location, biological behavior, molecular-genetic changes, and prognosis, which should be considered in diagnosis and treatment. The primary difference between aHGG and pHGG lies in *IDH 1/2* gene mutations, as well as *EGFR* gene expression, *TERT* promoter mutations, chromosomal changes (+7/−10), and *TP53* gene mutations, all of which are often associated with a poor prognosis in glioma patients. In contrast to aHGG, pHGG diagnostics and prognostics rely on changes in histone proteins H3.3 or H3.1 (H3.3 K27 and H3 G34).

Disclosure

Conflict of Interest

The authors declare no conflict of interest.

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