Review

Low-Grade Gliomas in Children

Abstract
Low-grade gliomas (LGG) are primary tumors of the central nervous system, originating from malignant transformation of cells in the brain or spinal cord. They are distinct from metastatic cancers that spread to the CNS from other parts of the body. While low-grade gliomas can occur throughout the nervous system, they are most commonly found in the cerebellum and central regions of the cerebrum, including the optic pathway and hypothalamic-pituitary axis. The growth of low-grade gliomas varies, with some tumors growing slowly and remaining localized, while others may progress rapidly and aggressively. Due to the limited space within the skull, the growth of a tumor can potentially damage critical areas of the brain, posing a risk to the patient's life. Although the risk of metastasis through the cerebrospinal fluid is generally low, children diagnosed with optic pathway gliomas at a young age may have a slightly increased risk of developing metastases. Research focus on new targets to treat this rare group of brain cancer in childhood.

Key Words
Glioma-child-low grade-treatment

Epidemiopathological aspects
Low grade gliomas are typically diagnosed between the ages of five and seven, with a higher incidence in children aged two to five (1-6). Boys are slightly more affected than girls, with a gender ratio of 1.1-1.3 to 1 (1-3). The incidence of LGG is 6.5/100000 inhabitants per year (2,3). In Germany, around 250 children and adolescents under 18 are diagnosed with low-grade glioma each year, with an incidence rate of 2 to 3 per 100,000 children (3,35). 20 per cent of all patients with LGG have an association with neurofibromatosis 1 (7). LGG include forms of sporadic cases and spontaneous regression (8,9,10,11,12,13). Low-grade gliomas are primary tumors of the central nervous system, originating from malignant transformation of cells in the brain or spinal cord. They are distinct from metastatic cancers that spread to the CNS from other parts of the body. While low-grade gliomas can occur throughout the nervous system, they are most commonly found in the cerebellum and central regions of the cerebrum, including the optic pathway and hypothalamic-pituitary axis (45). The growth of low-grade gliomas varies, with some tumors growing slowly and remaining localized, while others may progress rapidly and aggressively. Due to the limited space within the skull, a growing tumor can pose a threat to vital brain functions and become life-threatening. The risk of metastasis through the cerebrospinal fluid is generally low, except for children with optic pathway gliomas diagnosed at a young age, who may have a slightly increased risk. The large group of low-grade gliomas consists of various types of tumors that can be distinguished by their appearance under the microscope and their biological behavior, especially molecular genetic characteristics. Metastases are rarely found. The 5 years survival rate is 85-90 per cent (14,15). LGG were found most often in the cerebellum, cerebral in 15 percent, deep midline structures in 10-15 percent, optic pathways 5 percent and as brain stem glioma in 2-4 percent (14,15).

Genetic aspects
The *causes* of LGG pathogenesis focus on genetic changes on chromosome 7 (2,3). In a few cases, duplications of the 7q34 region were present with higher BRAF-1 expression and activation of RAS/RAF/MEK signal pathway (16). In 5-10 percent of all cases TP-53 mutations and nidogen-1 expression were described (17-19,42-43). Moreover, mutations of isocitrate dehydrogenase (IDH) with gain-or loss of function were found, resulting in high levels of 2-hydroxyglutarat as a *driver* of gliomagenesis (20-23).

Histological features
Low-grade gliomas develop from neuroglia that have become malignant. These cells provide support and protection for the brain's nerve cells (25). The exact cause of this transformation of glial cells into malignancy is not fully understood. It is known that children with certain inherited diseases, such as neurofibromatosis type 1 or tuberous sclerosis, have a higher risk of developing low-grade gliomas compared to healthy individuals. For example, up to 20% of patients with neurofibromatosis 1 develop a low-grade glioma within the first 20 years of life, often in the optic pathway or lower brain stem. Up to 15 percent of patients with tuberous sclerosis are diagnosed with subependymal giant cell astrocytoma, a specific subtype of low-grade glioma, before reaching adulthood. These genetic diseases that predispose individuals to cancer are known as cancer predisposition syndromes. Additionally, childhood brain radiotherapy, such as that received by patients with certain forms of leukemia or retinoblastoma, is linked to an increased risk of developing a CNS tumor later in life (25).

Classification (WHO)
The World Health Organization classifies low-grade gliomas as WHO-grade I or WHO-grade II tumors. High-grade gliomas (WHO-grade III and IV tumors) are highly malignant and are discussed separately on this website. WHO-grade I tumors are considered benign gliomas with slow growth and well-defined margins. These tumors may compress adjacent tissue but typically do not invade it. WHO-grade II tumors tend to grow diffusely into surrounding structures and spread more rapidly throughout the central nervous system. Transformation of low-grade gliomas into high-grade tumors, as seen in adults, is rare in children. Low-grade gliomas also vary in their degree of malignancy, with differences in growth rate and aggressiveness. Grade I is localized more at the brain stem region, Grade II LGG are more infiltrative. LGG are found supratentorial, pontin or infratentorial. From histological aspects, astrocytic, oligodendroglial and mixed glial-neuronal prominent forms of LGG were described.

Symptoms of LGG
The symptoms of low-grade gliomas vary depending on the patient's age, tumor location, size, and spread within the CNS. General and specific symptoms may be typical. General symptoms are nonspecific and can mimic other diseases. These symptoms may include headaches, back pain, dizziness, loss of appetite, nausea, vomiting, weight loss, fatigue, difficulty

concentrating, school issues, mood changes, and developmental delays. These symptoms are often caused by increased intracranial pressure due to the growing tumor within the skull or blockage of cerebrospinal fluid flow, leading to hydrocephalus. In infants, elevated intracranial pressure may present as a bulging fontanelle or macrocephalus. Specific symptoms depend on the tumor location and affected CNS regions. For example, a low-grade glioma in the cerebellum can cause dizziness and gait problems, while a tumor in the hemispheres may lead to seizures or motor deficits. Spinal cord tumors can cause back pain, muscle weakness, and numbness. Vision, mental, and sleep issues may also indicate tumor location.

Therapeutical aspects

There are currently no ongoing therapy optimization trials for children and adolescents with low-grade glioma in Germany. The last trial, SIOP-LGG 2004, closed for patient registration in early 2012, and a subsequent trial has not yet been initiated but is in the planning stages. From April 2012 to the end of 2018, children and adolescents with low-grade glioma were enrolled in the SIOP-LGG 2004 Registry. The LOGGIC Registry is an international registry available for patients with low-grade glioma in Germany (35). Since January 1, 2019, the LOGGIC Registry has been enrolling children and adolescents under 21 years of age in Europe who have newly diagnosed low-grade glioma (35). The LOGGIC Core Bio Clinical Data Bank, opened in April 2019, documents molecular tumor characteristics. The LOGGIC Registry and LOGGIC Core aim to collect comprehensive data, including molecular information, from patients with low-grade glioma to enhance understanding of tumor biology and facilitate the development of new treatment strategies (35). Given the excellent long-term survival prognosis associated with low-grade gliomas, all therapeutic considerations should prioritize preserving CNS function and the patient's quality of life.

New targets in therapy

The advancing *understanding of the biology* of LGG opens up possibilities for targeted therapy with small inhibitory molecules. For patients with NF1 and plexiform neurofibromas, the known molecular genetic abnormalities have already become the target of therapy. Since activation in the MAPK/ERK signaling pathway can be detected in 100% of pilocytic astrocytomas, targeted therapies have been used in initial studies after uncovering relevant feedback and escape mechanisms of pathway inhibition (27,29). MEK inhibitors BRAFV600E inhibitors and type II RAF inhibitors like Tovorafenib as well as a combination therapy of Dabrafenib and Trametinib represent promising classes of substances (37,40,41,44,47). Their value compared to conventional chemotherapy needs to be evaluated in future studies, as well as the acute, subacute, and long-term toxicities of these new substances. Recent research focus on a new target, vemurafenib, a protein kinase inhibitor (24).

Biomarkers

Biomarkers of LGG can be separated in *two groups*; group 1 with focused extension of LGG are Aquaporin-4, Nideogen-1-expression, BRAF-1-mutation and C11orf95-RELA-fusion; group 2 includes biomarkers in diffuse glioma like IDH ½, 1 p/19q Co-deletion, ATRX, TERT, FUBPI, FGFR3/TACC3 fusion, T2-FLAIR-mismatch, MYB/MYBL1-alteration and MIB-1 labeling index (18,24,30,31,33,34,37,38,40,44,46).

Follow-up diagnostics

Follow-up diagnostics and aftercare serve the oncological assessment of the course and the determination of the extent of functional losses and rehabilitation needs caused by the tumor and therapy. The type and frequency of examinations, such as visual and auditory testing, EEG and evoked potentials, endocrinological testing, blood count, and kidney function testing, must be tailored to the individual case and local conditions. To ensure psychosocial reintegration into everyday life, school, and work, extensive examinations and regular follow-up assessments of neuropsychological functions, quality of life, and adaptive behavior are of particular importance (32). This helps to identify cognitive late effects, as well as individual strengths and weaknesses, to implement targeted interventions derived from them, and thus improve children's participation in everyday life. In interdisciplinary care, especially neuropediatricians, neuropsychologists, psychologists, social workers, and teachers, in cooperation with physiotherapists, occupational therapists, and speech therapists, must be involved. School rehabilitation for often visually impaired children must be carried out with the involvement of country-specific institutions. The individual coping with the disease can be supported by psychotherapeutic care. The current need for such support should be continuously assessed in outpatient care by the responsible psychologist. Rehabilitation is often a long-term or continuous process that is primarily carried out on an outpatient basis and occasionally focused in rehabilitation clinics with specific expertise in the treatment of pediatric brain tumor patients through optimized diagnostic and therapeutic measures. Family-oriented rehabilitation also offers the opportunity to train parents in dealing with limitations, stabilize the entire family system regarding the frequent and long-term consequences of the disease, and develop life perspectives. Due to the long progression times of tumors, lifelong follow-up appears advisable for individual subgroups such as neurofibromatosis patients and patients with optic pathway gliomas with pituitary deficits, necessitating appropriate transition care.

Conclusion

Low-grade gliomas are slow-growing primary brain tumors that typically progress to a malignant state. Treatment involves surgical removal, possible chemoradiation for high-risk cases, and ongoing monitoring to delay progression and enhance quality of life (26,28,39). The approach for low-risk patients is less clear. Advances in molecular profiling will help refine risk assessment and prognosis for low-grade gliomas, leading to more personalized treatments that enhance survival and reduce side effects.

Disclaimer (Artificial intelligence)

The author hereby declares that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

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