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Chapter One - Pediatric-Type Diffuse Low Grade Glioma

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Abstract

Pediatric-type diffuse low grade glioma are a novel subgrouping of pediatric glioma defined in the updated WHO 2021 classification of central nervous system tumors. The newly recognized pediatric-type diffuse low grade glioma family is comprised of four distinct entities, including diffuse astrocytoma *MYB* or *MYBL1*-altered, angiocentric glioma, polymorphous low-grade neuroepithelial tumor of the young, and diffuse low grade glioma *MAPK*-altered. Due to significant overlap in histopathology and molecular alterations between pediatric-type diffuse low grade glioma, accurate diagnosis of these tumor subtypes requires integration of both histology and molecular findings. Herein, we describe the epidemiologic, imaging, and molecular features of these pediatric diffuse glioma. In addition, we review current knowledge regarding management approach and treatment outcomes, including potential therapeutic implications of prevalent molecular alterations within this family of tumors.

Introduction

Pediatric low-grade gliomas (pLGG) are the most common central nervous system (CNS) tumor of childhood (Group, 2008, Jacques and Cormac, 2013, Stiller et al., 2019), representing over 30% of all pediatric CNS tumors diagnosed in infants, children and young adults in the developed world (Ostrom et al., 2022, Ostrom et al., 2023). By definition arising from glial or mixed glial-neuronal cell lineages, pLGG are histologically benign tumors classified as either World Health Organization (WHO) grade I or II tumors with generally favorable long-term overall survival (OS) (Armstrong et al., 2011, Bale and Rosenblum, 2022a, Bandopadhayay et al., 2014, Fisher et al., 2008, Louis et al., 2021, Sievert and Fisher, 2009, Tonse et al., 2018, Youland et al., 2013).

PLGG is an umbrella term for a spectrum of many distinct tumor subtypes of varying histology, molecular aberrations, and clinical phenotypes (Table 1) (Bale and Rosenblum, 2022a, Hargrave, 2009, Sievert and Fisher, 2009, Wen and Packer, 2021). As such, there is variation between patient demographics, tumor location, tumor biology, and consequent tumor behavior across the many subtypes resulting in varying progression-free (PFS) and OS, as well as tumor and treatment-related morbidity impacting on individual patient function and quality of life (Aarsen et al., 2006, Bandopadhayay et al., 2014, Boele et al., 2015, Campanella et al., 2017, Kristiansen et al., 2019, Musial-Bright et al., 2011, Ryall et al., 2020, Ryall et al., 2020). This clinical and molecular heterogeneity often results in challenging therapeutic decision-making in clinical practice (Cooney et al., 2020, Green, 2024, Guerreiro Stucklin et al., 2016, Ryall et al., 2020).

Pediatric-type diffuse low-grade gliomas (pDLGG) are a noteworthy example of how advances in cancer diagnostic and molecular profiling technologies have transformed our understanding of this diverse set of tumors. Within the recently updated '2021 WHO Classification of Tumors of the Central Nervous System' (Bale & Rosenblum, 2022a), pDLGG represent a newly recognized pLGG tumor family comprising four distinct entities with similar histopathologic features but distinct clinical and epigenetic profiles:

1) Diffuse Astrocytoma, MYB or MYBL1-altered (MYB-DA)

2) Angiocentric Glioma (AG)

3) Polymorphous Low-Grade Neuroepithelial Tumor of the Young (PLNTY)

4) Diffuse Low-Grade Glioma, MAPK Pathway-Altered (pDLGG-MAPK)

While AG were first recognized as a distinct WHO grade 1 entity in the 2007 WHO CNS classification, the revised 2021 classification now defines AG within the group of pDLGG (Bandopadhayay et al., 2016, Camelo-Piragua and Kesari, 2016, Johnson et al., 2017, Komori et al., 2016, Louis et al., 2021, Qaddoumi et al., 2016), with the remaining three entities representing entirely novel tumor subtypes comprising the new pDLGG family (Table 1) (Bale & Rosenblum, 2022a). This chapter will review the molecular evolution of the recent classification of pDLGG and its facilitation of more clinically relevant integrated diagnoses, before reviewing each of the

four separate pDLGG entities, including evaluation of strategies for integrated diagnosis and the potential for precision-based therapies.

Section snippets

The molecular evolution of pediatric-type diffuse low-grade gliomas

The evolution of our insights and understanding of the genetic drivers underpinning pLGG formation through next-generation sequencing and deoxyribonucleic acid (DNA) methylation profiling has led to a revolution of pLGG tumor classification. The inclusion of molecular features within the 2021 WHO classification of CNS tumors seeks to increase diagnostic accuracy and further distinguish distinct low-grade glioma subtypes despite overlapping histopathological, molecular, and clinical features. …

An approach to integrated pDLGG diagnosis

An integrated approach to the diagnosis of pDLGG with clinical, histologic, and molecular context remains important for accurate diagnosis, given that many molecular alterations are not unique to a given pDLGG subtype. For example, *BRAF* mutations and *FGFR* aberrations are observed in both PLNTY and MAPK-DLGG, and MYB/MYBL1 alterations are observed in both MYB-DA and AG (Bandopadhayay et al., 2016, Fabbri et al., 2022, Louis et al., 2019, Pollack et al., 2019, Ryall et al., 2017). Accordingly, …

Epidemiology and clinical presentation

As implied by its name, *MYB*- or *MYBL1*-altered diffuse astrocytoma (MYB-DA) are a rare subtype of pDLGG harboring recurrent *MYB* or *MYBL1* alterations and are therefore closely molecularly related to angiocentric glioma (AG) (Chiang et al., 2019, Ellison et al., 2019, Qaddoumi et al., 2016). However, given their lack of the classic morphological characteristics of AG, MYB-DA have now been classified as a separate, distinct pDLGG entity (Chiang et al., 2019, Ramkissoon et al., 2013, Zhang et al., …

Epidemiology and clinical features

Angiocentric glioma (AG) are exceptionally rare pDLGG typically presenting in the first or second decade of life (Ryall, Zapotocky, et al., 2020). Nearly all AG have a *MYB-QKI* gene fusion, with the remainder harboring a different *MYB* alteration. AG occur most commonly in the supratentorial location (predominantly cerebral cortex), with an increasing number of reports describing AG within the brainstem. Clinical manifestations of AG include focal deficits related to the anatomic area of …

Epidemiology and clinical features

Polymorphous low-grade neuroepithelial tumor of the young (PLNTY) is a recently defined, rare low-grade neuroepithelial tumor typically presenting during adolescence with a median age of 16 years (Huse et al., 2017). PLNTY localize most frequently to the temporal lobe with both cortical and subcortical components and are considered to belong to the group of long-term epilepsy associated tumors (Huse et al., 2017, Johnson et al., 2019). As these tumors are commonly epileptogenic, most …

Epidemiology and clinical features

pDLGG pathway-altered are low grade neoplasms with diffuse astrocytic or oligodendroglial morphology that typically occur in childhood and are characterized by alterations in the genes coding for MAPK pathway proteins. The Ras-Raf-MAPK pathway is a critical intracellular signaling pathway that regulates cell growth, proliferation, and survival. Molecular alterations of the Ras-Raf-MAPK pathway are the most prevalent oncogenic drivers of pLGG, occurring in nearly 85 % of sequenced tumors (Ryall, …

Conclusion

Diffuse pediatric-type LGG are a newly defined and rare group of CNS tumors that require integration of both histologic and molecular features for accurate diagnosis. While pLGG have historically represented a diverse group of tumors, inclusion of PLNTY, AG, pDLGG *MAPK*-altered, and diffuse astrocytoma *MYB/MYBL1*-altered in the revised 2021 WHO classification has further subcategorized LGG in children. The substantial histologic and molecular overlap between both circumscribed and subcategories …

Volume chapters

References (107)

B.A. Greenberger *et al.*
Clinical outcomes and late endocrine, neurocognitive, and visual profiles of proton radiation for pediatric low-grade gliomas
International Journal of Radiation Oncology, Biology, Physics (2014)

G. Jacques *et al.*
Central nervous system tumors
Handbook of Clinical Neurology (2013)

D. Planchard *et al.*
Dabrafenib plus trametinib in patients with previously treated BRAF(V600E)-mutant

metastatic non-small cell lung cancer: An open-label, multicentre phase 2 trial
The Lancet Oncology (2016)

H. Sumdani *et al.*
Case report of rarely described polymorphous Low-Grade neuroepithelial tumor of the young and comparison with oligodendroglioma
World Neurosurgery (2019)

F.K. Aarsen *et al.*
Functional outcome after low-grade astrocytoma treatment in childhood
Cancer (2006)

M.K. Aghi *et al.*
The role of surgery in the management of patients with diffuse low grade glioma: A systematic review and evidence-based clinical practice guideline
Journal of Neuro-Oncology (2015)

A.O. Almubarak *et al.*
Angiocentric glioma of brainstem
Neurosciences (Riyadh) (2020)

M.K. Andersson *et al.*
Targeting the oncogenic transcriptional regulator MYB in adenoid cystic carcinoma by inhibition of IGF1R/AKT signaling
Journal of the National Cancer Institute (2017)

A.A. Apfelbaum *et al.*
LGG-02. Elucidating the role of fgfr1 alterations in pediatric gliomas
Neuro-Oncology (2024)

G.T. Armstrong *et al.*
Survival and long-term health and cognitive outcomes after low-grade glioma
Neuro-Oncology (2011)

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