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Review

# Pediatric high grade gliomas: A comprehensive histopathological, immunohistochemical and molecular integrated approach in routine practice

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## Abstract

Pediatric high grade gliomas have undergone remarkable changes in recent time with discovery of new molecular pathways. They have been added separately in current WHO 2021 blue book. All the entities show characteristic morphology and immunohistochemistry. Methylation data correctly identifies these entities into particular group of clusters. The pediatric group high grade glioma comprises- Diffuse midline glioma, H3K27-altered; Diffuse hemispheric glioma, H3G34-mutant; Diffuse pediatric-type high-grade glioma, H3-wild type & IDH-wild type; Infant hemispheric glioma and Epithelioid glioblastoma/Grade 3 pleomorphic xanthoastrocytoma and very rare IDH-mutant astrocytoma. However it is not always feasible to perform these molecular tests where cost-effective diagnosis is a major concern. Here we discuss the major entities with their characteristic histopathology, immunohistochemistry and molecular findings that may help to reach to suggest the diagnosis and help the clinician for appropriate treatment strategies. We have also made a simple algorithmic flow chart integrated with histopathology, immunohistochemistry and molecular characteristics for better understanding.

## Introduction

Central nervous system (CNS) tumors stand as the foremost solid neoplasms encountered in childhood, presenting a formidable frontier in pediatric oncology [1]. Within this domain, gliomas emerge as a prominent entity, accounting for approximately half of all cases, characterized by a spectrum of clinical manifestations and prognostic outcomes [1].

Incidence of pediatric low grade gliomas are more than high grade gliomas [2]. Low grade gliomas are pilocytic astrocytoma, ganglioglioma, pleomorphic xanthoastrocytoma, Diffuse low grade glioma MYB1 altered, angiocentric glioma and Diffuse low grade glioma, MAPK-pathway altered [3], [4].

High grade gliomas comprise of heterogenous groups of tumors. With the advancement of methylation profiling, there have been considerable change in the understanding and classification of this group of tumor. For improvisation of diagnosis and proper classification, cIMPACT (The Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy) was formed in 2016 by a group of neuropathologists and neuro-oncologists [5]. In latest WHO CNS 2021 blue book, pediatric -type diffuse high grade glioma have been separately described [6].

This category encompasses four subgroups-

1. Diffuse midline glioma, H3K27-altered.
2. Diffuse hemispheric glioma, H3G34-mutant.
3. Diffuse pediatric type high grade glioma, H3-wild type and IDH-wild type.
4. Infant type hemispheric glioma.

Other high grade gliomas in pediatric age group are

5. Epithelioid glioblastoma / Pleomorphic xanthoastrocytoma, grade 3.
6. IDH mutant astrocytoma, grade 3/4

Here we describe in details how to reach the diagnosis with histopathology and immunohistochemistry especially when further molecular testing is not available or feasible.

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## Section snippets

### Diffuse midline glioma (DMG), H3K27-altered

Diffuse midline glioma is defined as infiltrating midline glioma with loss of H3K27Me3 and H3K27M mutation (H3c.83A>T p.K28M K27M), aberrant overexpression of EZHIP, or an EGFR mutation (CNS WHO grade 4).

The tumor must show diffusely infiltrating growth in the CNS parenchyma, localizing in the midline structures (thalamus, brainstem and spinal cord) and demonstrate one of the molecular alteration described above [5]. Previously it used to be called as Diffuse intrinsic pontine glioma (DIPG).

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### Diffuse hemispheric glioma (DHG), H3G34-mutant

Diffuse hemispheric glioma, H3G34-mutant is an infiltrative glioma that involves cerebral hemispheres, with

missense mutation of the H3–3A gene that causes substitution of histone H3 protein- c.103G>A p.G35R (G34R), c.103G>C p.G35R (G34R) or c.104G>T p.G35V (G34V) (CNS WHO grade 4).

Adolescent and young adult population are commonly affected [15].

Imaging of this group is like any other non-midline glioblastoma showing contrast-enhancing tumor with mass effect in cortical area [16].

Histopathology …

## Diffuse pediatric-type high-grade glioma (pHGG), H3-wild type, IDH-wild type

It is an infiltrating glioma that typically occurs in children, adolescent and young adult and is wild type for H3K27M, EZHIP, EGFR, H3G34R, H3G34V, IDH1 & IDH2.

Exact epidemiological data for this entity does not exist [6]. As in the name, this group is typically seen in children, adolescent and young adult. However it can be seen in adult and older age group also as data on adult population is underestimated [19]. This tumor may arise after therapeutic radiation or in the context of germline…

## Infant type hemispheric glioma

Infantile hemispheric glioma (IHG) is a high-grade astrocytic tumor that typically emerges in early childhood. It is characterized by receptor tyrosine kinase (RTK) fusions, with frequent involvement of the NTRK family, ALK, ROS1, or MET genes.

Typically seen in early childhood, mostly in first year of life. Most common location of this tumor is supratentorial location with frequent leptomeningeal involvement [23].

Based on the fusion genes, this group of tumor is subdivided into following these…

## Epithelioid glioblastoma and pleomorphic xanthoastrocytoma grade 3

Epithelioid glioblastoma (eGB) is characterized by solid aggregates of epithelioid cells having abundant eosinophilic cytoplasm and eccentric nuclei and characteristic BRAF V600E mutation [26].

This entity was first described in 2016 WHO Book as a separate entity however in recent WHO 2021 Blue book it has been kept under subtype of IDH Wild type glioblastoma [27].

Epithelioid glioblastoma predominantly seen in children and young adult while it can be seen in adult and rarely in older age group.

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## IDH mutant astrocytoma

IDH mutant astrocytoams are extremely rare in children. Morphology is like adult astrocytoma showing IDH mutation (IDH1/2), ATRX mutation and p53 mutation.

The flow Chart 1 and 2 have been added.…

## Conclusion

Pediatric high grade gliomas show dismal prognosis.

Radiation therapy, coupled with resection whenever feasible, stands as the cornerstone of standard care for all pediatric high-grade gliomas (HGGs). Resection, in particular, confers the most substantial advantage in overall survival (OS), irrespective of supplementary treatment modalities [34], [35]. The efficacy of targeted therapies is poised to show good result when tailored to specific subgroups boasting pertinent molecular alterations....

## Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used ChatGPT only for two sentences in Conclusion part in order to better representation and make it user friendly. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication....

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