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| REVIEW

Pediatric High-Grade Astrocytoma With Piloid Features: A Comprehensive Literature Review

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ABSTRACT

Background: High-grade astrocytoma with piloid features (HGAP) is a recently defined central nervous system (CNS) tumor, first introduced into the 2021 World Health Organization (WHO) classification. While predominantly observed in adults, pediatric cases remain rare and poorly characterized. This study aimed to review the epidemiology, clinical features, and molecular profile of pediatric HGAP.

Methods: A comprehensive review of studies published from 2018 to 2025 was performed to identify methylation-confirmed HGAP cases in patients aged 18 years or younger. Data extracted from studies included subject demographics, tumor location, histological features, molecular alterations, and the implemented treatment sequence.

Results: The search identified 17 pediatric cases meeting the inclusion criteria. The median age at diagnosis was 15 years (range: 4-18 years), and a male predilection of approximately twofold was observed. Tumors most commonly arose in the posterior fossa (56.3%). Recurrent molecular alterations included *CDKN2A/B* loss (75%), FGFR1 mutations or fusions (55.6%), and ATRX loss (45.5%).

Conclusion: This review did not identify definitive clinical or histomolecular differences between pediatric and adult HGAP, underscoring the need for further comparative studies. Pediatric HGAP may represent an underrecognized diagnostic entity within the glioma spectrum, emphasizing the critical role of methylation profiling for accurate diagnosis and classification. Retrospective reclassification of histologically and molecularly ambiguous gliomas is warranted and may reveal additional cases. Larger pediatric cohorts are urgently needed to inform clinical management and refine prognostic stratification.

Abbreviations: ATRX, alpha thalassemia/mental retardation syndrome X-Hnked; CDKN2A/B, cyclin-dependent kinase inhibitor 2A/B; CNS, central nervous system; FGFR1, fibroblast growth factor receptor 1; GEM, glioblastoma; *HGAP,* high-grade astrocytoma with piloid features; *IDH, isocitrate dehydrogenase; LOG,* low-grade glioma; MAPK, mitogen-activated protein kinase; MR, magnetic resonance; NF1, neurofibromatosis type 1; OS, overall survival; FA, pilocytic astrocytoma; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PTPN11, protein tyrosine phosphatase, non-receptor type 11; RT, radiation therapy; VEGFA, vascular endothelial growth factor A; WHO, World Health Organization.

1 | Introduction

Genome-wide methylation profiling has provided invaluable insight into the epigenetic landscape of cancer. The identification of methylation patterns that are tumor-intrinsic and biologically distinct has aided in the reclassification of central nervous system (CNS) tumors. High-grade astrocytoma with piloid features (HGAP) is a recently recognized entity that was introduced into the 2021 World Health Organization (WHO) classification of CNS tumors. Diagnosis of HGAP is based on its unique DNA methylation profile [1]. Reinhardt et al. were the first to describe HGAP—formerly referred to as anaplastic astrocytoma with piloid features—as a novel molecular class of isocitrate dehydrogenase (IDH) wild-type glioma, harboring recurrent mitogen-activated protein kinase (MAPK) pathway, *CDKN2A/B* (cyclin-dependent kinase inhibitor 2A/B), and *ATRX* alterations (alpha thalassemia/mental retardation syndrome X- linked) [2]. There is an overall lack of published HGAP studies, and available cohorts have reported only a limited number of pediatric cases [2-4], The reported median age at diagnosis is 43 years, with a range of 4-88 years [3]. This raises the question of whether the clinical and molecular characteristics described in predominantly adult populations are applicable to pediatric patients [4], This review compiles and analyzes all currently published, methylation-confirmed pediatric HGAP cases with the aim of better understanding this rare tumor subtype in children and adolescents.

2 | Methods

To conduct this literature review on pediatric HGAP, we performed an advanced search on PubMed using the following terms: “hgap” OR “high-grade astrocytoma with piloid features” OR “high-grade astrocytoma with piloid features” OR “anaplastic pilocytic astrocytoma” OR “anaplastic astrocytoma with piloid features” OR “methylation-class anaplastic astrocytoma” OR “methylation class anaplastic astrocytoma.” This search yielded 228 publications as of March 13, 2025. Studies selected for inclusion were published as early as 2018, following the first description of HGAP by Reinhardt et al. [2], A total of 129 publications were ultimately reviewed. Of these, five publications included pediatric cases of HGAP, defined as HGAP diagnosed in patients 18 years of age and younger. Cases were only included if they were confirmed by DNA methylation profiling. When reported, classifier versions and calibrated scores were documented, with scores >0.84 considered high-confidence matches. In cases with discordant scores between methylation classifiers, inclusion was considered based on the presence of additional supportive molecular features for HGAP (i.e., MAPK pathway activation, CDKN2A/B homozygous deletion, ATRX loss, TP53 mutation). One case with discordant methylation classifier scores and lacking other supportive molecular alterations was excluded from the final cohort. When available, we reviewed subject demographics (age at diagnosis, sex), clinical features (tumor location, presentation—primary vs. recurrence), magnetic resonance (MR) imaging characteristics, surgical intervention (biopsy vs. resection—gross total or subtotal), treatment sequence, progression-free survival (PFS), overall survival (OS), histopathology, and molecular characteristics. PFS was defined as the interval from the date of initial surgery to clinical and/or radiographic evidence of progression. OS was defined as the interval from initial surgery to death.

3 | Results

Our review identified 17 cases of HGAP in patients aged 18 years or younger. The largest published HGAP cohort reported that 9% (12/135) of cases were pediatric [3]. A separate cohort (n = 76) of tumors reclassified as HGAP with an initial histologic diagnosis of anaplastic pilocytic astrocytoma (PA) found that 11% were diagnosed in individuals under 20 years of age [2]. Another study presenting 27 HGAP cases, out of a total of 86 cases originally diagnosed as cerebellar glioblastoma (GBM), reported one pediatric patient [5]. Interestingly, a pediatric cohort of 31 anaplastic PA cases identified only a single case of HGAP, with the majority (77%) matching to pilocytic astrocytoma on methylome [4] (Table 1).

Across these studies, there was heterogeneity in the level of reported case-specific data. As a result, the total number *(n)* of reported cases varied across data entities. The median age at diagnosis was 15 years (range: 4-18 years) (Figure la). There was a male predilection, with 64.7% of cases occurring in males and 35.3% in females. The most common tumor location was the posterior fossa (56.3%), followed by supratentorial regions (31.3%), and the spinal cord (12.5%) (Figure lb). Concomitant neurofibromatosis type 1 (NF1) syndrome was reported in two of 18 patients (12.5%). One HGAP patient had underlying Noonan syndrome [6].

High confidence scores (>0.84) were reported in all 15 pediatric cases with available methylation data. Cimino et al. identified three epigenetic subtypes based on methylation clustering: gl, g2, and gNFl [3]. Within our pediatric cohort, the distribution of reported subtypes was gl in 58.3% (7/12), g2 in 33.3% (4/12), and gNFl in 8.3% (1/12). The most frequently identified genetic alteration was *CDKN2A/B* loss, present in 75% (12/16) of tumors. *FGFR1* (fibroblast growth factor receptor 1) alterations (mutation or fusion) were reported in 55.6% (5/9) of cases. *ATRX* (alpha thalassemia/mental retardation syndrome X- linked) loss or mutation was reported in 45.5% (5/11). Additional alterations included *NF1* mutation or deletion in 36.4% (4/11), *MGMT* (06-methylguanine-DNA methyltransferase) promoter hypermethylation in 66.7% (2/3), and *BRAF-K1AA1549* fusion in 10% (1/10) (Table 2).

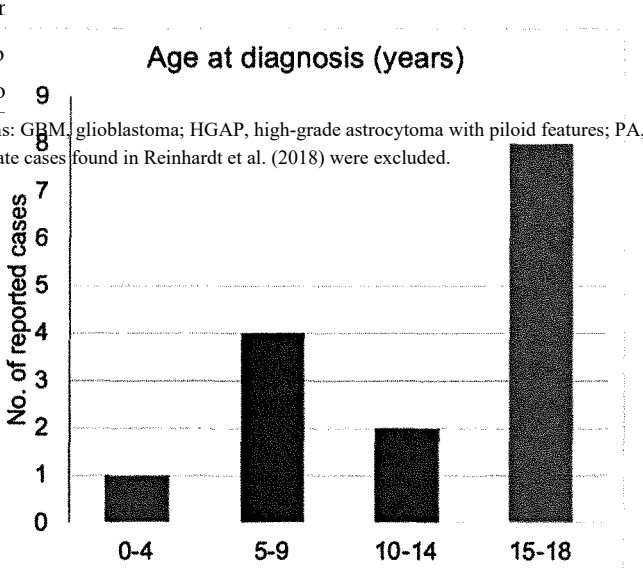
Histological features were reported in a minority of cases *(n* = 8). Among these tumors, histological diagnoses included: anaplastic PA (5/8), cerebellar GBM (1/8), low-grade glioma (LGG) without anaplasia (1/8), and oligodendroglial-like morphology (1/8). Tumor status of HGAP, whether a primary or recurrent growth, was specified in 12 cases, with 75% (9/12) reported as primary tumors and 25% identified in the recurrent setting (3/12).

The treatment sequence was described in only two of 21 cases, both of which involved surgical resection followed by postoperative radiotherapy (RT) or adjuvant chemotherapy plus RT [6], Prognostic data were limited; PFS and OS were reported in nine of 17 and eight of 17 cases, respectively. The mean PFS was 32 months, and the mean OS was 44.9 months.

TABLE 1 I Studies with reported cases of pediatric HGAP confirmed via methylation

Publication, year	Cohort	Pediatric cases (No.)
(1) Reinhardt et al., 2018	Reanalysis of 120 cases of histologically defined anaplastic PA	6
(2) Reinhardt et al., 2019	Reanalysis of 86 posterior fossa tumors previously diagnosed as cerebellar GBM	1
(3) Garetor		
(4) Cimino		
(5) Staunto		

Abbreviations: GBM, glioblastoma; HGAP, high-grade astrocytoma with piloid features; PA, pilocytic astrocytoma; PAAF, pilocytic astrocytoma with anaplastic features.
'Four duplicate cases found in Reinhardt et al. (2018) were excluded.



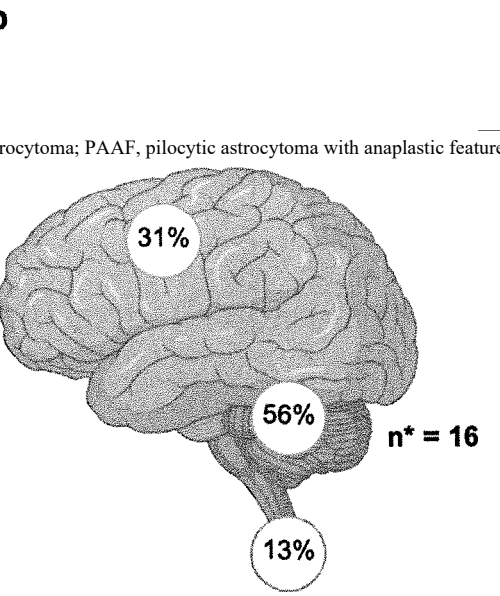


TABLE 2 I Summary of clinical characteristics and molecular alterations[2] in pediatric HGAP cases.

4 | Discussion

HGAP is a recently recognized tumor entity, first described in the 2021 CNS WHO, based on its distinct DNA methylation profile [1]. It is an IDH-wildtype astrocytic tumor with variable histologic features, but generally harboring "piloid" phenotype and anaplasia. Methylation profiling is currently required for diagnosis, while the presence of *CDKN2A/B, ATRX,* and MAPK pathway alterations is suggestive but not diagnostic. Nevertheless, available literature in the pediatric population is scarce, and a better understanding of this entity is warranted.

While HGAP occurs predominantly in adults, when identified in pediatric patients, it appears to present most commonly during adolescence. A male predilection of approximately twofold was observed, though the limited cohort size restricts interpretation of sex-based differences. Notably, Cimino et al. reported a slight male predominance (1:1.44), while Reinhardt et al. reported a balanced sex distribution [2, 3]. Across age groups, tumors most frequently arise in the posterior fossa and typically involve midline structures. The two largest predominantly adult cohorts reported a higher percentage of posterior fossa tumors (74% and 62%), with fewer supratentorial (17% and 26%) and spinal cord (7% and 10%) tumors, compared to our pediatric cohort [2, 3]. Despite this midline predilection, HGAP can be easily distinguished from diffuse midline glioma due to its distinct molecular alterations characterized by H3K27M/EGFR mutation or EZHIP overexpression [7, 8].

In our review, *CDKN2A/B* loss (12/16) was the most frequent alteration, followed by *ATRX* loss (5/11), while *FGFR1* mutation or fusion (5/9) was the most common MAPK pathway alteration. These findings are generally consistent with adult cohorts, which report even higher frequencies of *CDKN2A/B* loss (88%) and *ATRX* mutations (65%). In these adult studies, *NF1* mutations were the most common MAPK pathway alterations (40%), while *FGFR1* mutations or fusions (19% and 14%, respectively) were the second most common. *BRAF* fusions (19%) and *MGMT* promoter hypermethylation (45%) are also reported [7], Interestingly, a prior study examining pilocytic astrocytomas with anaplastic

TABLE 2 I Summary of clinical characteristics and molecular alterations[2] in pediatric HGAP cases.

				CDKN2A/B mut/del	ATRX loss/mut	NF1 mut/del	FGFR1 mut/fus	MGMT promoter meth	BRAF/ KIAA1549 fiis	BRAF V600E mut
Reinhardt et al.	F	18	PF							
(2018)	F	4	SC							
	M	0-18	PF							
	M	6	PF							
	M	0-18	PF							
Reinhardt et al. (2019)	M	5	PF							
Gareton et al.	F	8	ST							
Cimino et al.	M	16	ST							
	M	14	PF							
	F	IS	ST							
	F	18	PF							
	M	17	ST							
	M	7	PF							
	F	17	n/a							
	M	16	ST							
	M	11	PF							
Staunton et al.	M	17	SC							

Abbreviations: ATRX, alpha thalassemia/mental retardation syndrome X-linked; CDKN2A/B, cyclin-dependent kinase inhibitor 2A/B; del, deletion; F, female; FGFR1, fibroblast growth factor receptor 1; fus, fusion; HGAP, high-grade astrocytoma with piloid features; M, male; MGMT promoter meth, 06-methylguanine- DNA methyl transferase promoter methylation; mut, mutation; n/a, not available; NF1, neurofibromatosis type 1; PF, posterior fossa; SC, spinal cord; ST, supratentorial.
'Correspondingyellow fields represent the presence of molecular alteration, green fields represent the absence of alteration, and gray fields represent an unknown status.

features (PAAF) also found a lower incidence of *CDKN2A/B* loss and *ATRX* loss in pediatric cases compared to their adult counterparts [4], Further interpretation of our results is limited by the small sample size and the heterogeneity of gene panels used across studies, which prevented a complete assessment of all relevant mutations. Further studies with larger pediatric cohorts are needed to determine if age-related molecular distinctions exist in HGAP.

A higher incidence of HGAP in patients with NF1 has been observed, consistent with our pediatric findings [3,9], As NF1 is a negative regulator of the MAPK pathway, bilallelic inactivation results in MAPK pathway hyperactivation. Of note, a case of HGAP in a patient with *PTPN11* (protein tyrosine phosphatase, non-receptor type ll)-associated Noonan syndrome reported four MAPK pathway aberrations, including two NF1 loss-of-function variants, a novel germline *PTPN11* mutation, and an FGFR1 mutation. Differential expression of *VEGFA* (vascular endothelial growth factor A) and programmed death-ligand 1 *(PD-L1)* was also identified as a potential therapeutic target [6].

Most published HGAP cases were diagnosed at initial presentation via methylation profiling, although rare instances of transformation from PA have been described [3], In one report, a 12-year-old patient with a posterior fossa PA confirmed via methylation profiling re-presented at age 27 with recurrent disease that was classified as HGAP [10], In another case, a 20-year-old with a basal ganglia-thalamic PA experienced recurrence 6 years later, with methylation analysis confirming HGAP [11], These cases suggest that HGAP may result from the transformation of a lower grade to a higher grade glioma, reinforcing the need to identify potential precursor lesions and predictive molecular signatures [12].

Radiographic characteristics of HGAP are poorly defined, and data regarding treatment responses and long-term outcomes remain limited [13], Available evidence suggests that overall survival (OS) for HGAP lies between that of PA and IDH-wildtype GBM (CNS WHO Grade 4) [3].

The rarity of HGAP, combined with its recent formal recognition, likely contributes to the paucity of clinical and epidemiologic data. To address these gaps, we have received Institutional Review Board approval to conduct a multi-institutional retrospective analysis of pediatric HGAP. We are currently collaborating with institutions both nationally and globally to collect and analyze unpublished, methylation-confirmed pediatric HGAP cases. Given that methylation profiling is not routinely performed in all institutions, it is likely that HGAP is underdiagnosed in children. We are actively pursuing funding for retrospective methylation testing on suspected HGAP cases from around the world, which will include patients with atypical LGG and anaplastic PA. Our

review underscores the need for future studies to better define the clinical, histologic, and molecular features of HGAP in the pediatric age group and establish a framework for standardized diagnosis and treatment.

Author Contributions

D.K.: study design, data gathering, data analysis, data interpretation, writing of primary draft, figure design. S.D., B.W.: review of histopathological material, figure design. S.D.: critical revision of the manuscript. A.M.: review of neuroimaging, interpretation of radiographic findings. M.S.A.: conceptualization, study design, supervision, data interpretation, critical revision of the manuscript. All authors reviewed and approved the final version of the manuscript.

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Conflicts of Interest

M.S.A. reports the following disclosures: consultant and speaker for Day One Biopharmaceuticals; consultant for Ipsen Pharmaceuticals; member of the advisory board for Day One Biopharmaceuticals; received provision of drug for research use from Novartis Pharmaceuticals; and received research funding from the National Cancer Institute (NCI), CureSearch Foundation, Rally Foundation, and Solving Kids Cancer.

The remaining authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new datasets were generated or analyzed during the current study.

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