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RESEARCH

Pubertal development and hormonal modulation in pediatric low-grade gliomas: a retrospective cohort study

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Abstract

Background Pediatric low-grade gliomas (pLGGs) are the most common brain tumors in children. While overall survival is excellent, tumor progression remains frequent, especially in surgically challenging locations. Puberty brings profound hormonal changes, and growing evidence suggests that sex hormones may influence glioma biology. The impact of pubertal development, including central precocious puberty (CPP), on tumor behavior is not well understood.

Methods We performed a retrospective study of 301 children with histologically confirmed pLGGs treated at a single tertiary center from 2015 to 2025. Data collected included clinical, radiological, endocrine, histopathological, and molecular information. Pubertal status was assessed using Tanner staging, and CPP was defined by standard clinical and hormonal criteria. Progression-free survival (PFS) was analyzed according to pubertal stage and, in patients with CPP, by treatment with gonadotropin-releasing hormone (GnRH) analogues. Kaplan–Meier curves and log-rank tests were used for survival analysis.

Results Advanced pubertal development (Tanner stage > 3) was observed in 112 patients (37%), and 18 patients (6%) met criteria for CPP. Nearly all children with CPP had tumors involving the diencephalic or hypothalamic–optic pathway. Among patients with CPP, those treated with GnRH analogues ($n = 13$) had significantly longer PFS than untreated patients ($n = 5$) ($p = 0.00038$), with 60-month PFS of 78% versus 25%. Tumor progression after stopping GnRH therapy often coincided with pubertal reactivation. Compared with age-matched children without CPP, GnRH therapy showed a trend toward longer PFS, though not statistically significant ($p = 0.10$).

Conclusions Pubertal development and CPP are strongly associated with hypothalamic–optic pathway pLGGs and may influence tumor behavior in a subset of patients. In children with CPP, hormonal suppression with GnRH analogues was associated with prolonged PFS, supporting a potential modulatory role of endocrine signaling in pLGGs. These findings underscore the importance of systematic monitoring of pubertal development and warrant prospective studies to clarify the role of endocrine modulation within multimodal treatment strategies for pediatric low-grade glioma.

Key points

- Pubertal stage is associated with modulation of the clinical course of pediatric low-grade gliomas.
- In children with central precocious puberty, treatment with GnRH analogues is associated with improved progression-free survival.
- Hormonal status and tumor location emerge as clinically relevant determinants of prognosis and should be considered in patient assessment and treatment planning.

Keywords Pediatric low-grade glioma · Early puberty · Sex hormones · Neuro-oncology · Endocrinology

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Introduction

Pediatric lowgrade gliomas (pLGGs) are the most common central nervous system (CNS) tumors in children, representing ~30–40% of all pediatric brain tumors worldwide Classified as World Health Organization (WHO) grade 1 or 2 and comprising a heterogeneous spectrum of histopathological subtypes—most notably pilocytic astrocytomas [1, 2]. Compared with adult lowgrade gliomas, pLGGs follow a more indolent clinical course, display a lower propensity for malignant transformation, and achieve excellent overall survival, with 5 year overall survival (OS) rates approaching 97% and 10 to 20 year OS around 90%. Nevertheless, progressionfree survival (PFS) is suboptimal, particularly in patients with residual disease or tumors in surgically challenging locations, where PFS ranges from 45% to 65% [3].

Clinical management is complicated by the wide anatomical distribution of these tumors—from the cerebellar hemispheres to deep midline structures such as the thalamus, hypothalamus, and brain-stemand by the morbidity associated with neurological deficits, endocrine dysfunction, and reduced quality of life (QoL). Surgery remains the preferred first-line treatment and gross total resection (GTR) often confers cure or durable control when feasible [4, 5]. However, many tumors are unresectable or only partially resected due to proximity to eloquent brain regions, necessitating adjuvant chemotherapy, radiotherapy, and increasingly molecularly targeted agents [6].

At the molecular level, pLGGs are driven predominantly by aberrations in the RASRAFMEKERK (MAPK) signaling cascade. The most frequent alterations include *BRAF* fusions (e.g., *KIAA1549BRAF*), *BRAF* mutations, *NF1* inactivation, and other less common events, all of which constitutively activate MAPK signaling to promote tumor growth and survival [7, 8]. This knowledge has transformed therapy: inhibitors targeting BRAF and MEK have demonstrated promising activity in progressive or recurrent disease [2, 4].

Puberty is characterized by surging sexhormone levels that may modulate pLGG behavior [9, 10]. These tumors express estrogen receptors (ERα, ERβ, GPER1), androgen receptor (AR), and possibly progesterone receptor (PR) [11–13]. ERα promotes proliferation, survival, and angiogenesis via PI3K/AKT/mTOR and MAPK/ERK signaling. In contrast, ERβpredominant in the CNS exerts tumorsuppressive effects through apoptosis induction and cellcycle arrest. GPER1, a membrane-bound estrogen receptor, activates rapid non-genomic pathways via cAMP and calcium, enhancing proliferation [11, 14, 15]. AR drives expression of growth-related genes and oncogenic pathways [13]. The PR function does not have a well-defined role in tumor progression. Collectively, these observations implicate sex hormones as modulators of low-grade glioma biology and potential targets for hormone-based therapies. Despite these advances, pubertal state and hormonal influences on pLGG biology remain underexplored.

Clinical evidence supports hormonal influence in LGGs: tumor regression after hormonal blockade has been reported in patients with precocious puberty and opticpathway gliomas. Kang *et al.* described partial regression of a pontine lesion following pubertal suppression with Gonadotropin-releasing hormone (GnRH) analogue alone [16]. Likewise, a 2-year-old girl exhibited > 50% reduction in the solid component of a low-grade brain tumor three years after GnRH analogue treatment for precocious puberty [17]. Pregnancy affords further insight: dramatic increases in estrogen and progesterone correlate with accelerated glioma growth [18]. A series from Nancy Hospital documented accelerated growth in 75% and increased seizures in 40% of 11 pregnant women with grade 2 gliomas [19]. More recent analyses by Peeters and Van Westrhenen showed tumor acceleration in 87% of pregnancies with early clinical decline in 38%, even in grade 2–4 gliomas—effects likely attributable to hormone levels rising up to 200-fold [19, 20]. Numerous invitro and invivo studies have subsequently sought to mechanistically validate these observations. Whether pubertal hormonal shifts causally drive tumor initiation or progression—or merely reveal an intrinsic biological susceptibility—remains unresolved.

Given the chronic nature of pLGGs and their frequent diagnosis during childhood and adolescence, disentangling the relationship between pubertal development and tumor biology is essential. Insights could refine prognostication, optimize the timing of intervention, and inspire novel therapeutic strategies incorporating endocrine modulation. Against this background, we undertook a retrospective analysis of pediatric patients with pLGG treated at our center. We examined associations between pubertal status (Tanner staging) and tumor dynamics, integrating clinical, radiological, and hormonal parameters with contemporary molecular data. Our objective is to elucidate the potential causal or mechanistic role of sex hormones in pLGG pathophysiology, thereby informing future translational and therapeutic approaches.

Materials and methods

This retrospective observational study was conducted at Bambino Gesù Children's Hospital and covered ten years (from January 2015 to December 2025). The study protocol received approval from the institutional review board, and all procedures adhered to the principles of the Declaration

of Helsinki. Informed consent for data collection and analysis was obtained from the legal guardians of all patients.

We included pediatric patients aged 1 to 18 years who had a histologically confirmed diagnosis of low-grade glioma (WHO grade 1 or 2) and who were treated at our institution during the study period. Eligible patients were required to have clinical, radiological, and hormonal follow-up data available for at least 12 months after diagnosis, as well as documented pubertal status assessed by Tanner staging at diagnosis and/or during follow-up.

Clinical data were retrospectively extracted from electronic medical records and included demographic information (age at diagnosis, sex), presenting symptoms, neurological status, and endocrine abnormalities. Tumor characteristics such as anatomical location, size, histological subtype, and molecular profile were recorded. Details of treatment, including the extent of surgical resection, chemotherapy regimens, radiotherapy, and any hormone-modulating therapies, were systematically collected.

Pubertal status was evaluated by experienced pediatric endocrinologists during routine clinical visits using Tanner staging, which assesses secondary sexual characteristics on a scale from stage 1 (prepubertal) to stage 5 (fully mature) [21]. Hormonal assays, including serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, testosterone, and other relevant markers, were used to confirm pubertal status or diagnose precocious puberty. Radiological follow-up was performed with magnetic resonance imaging (MRI) scans, and tumor size and progression were assessed according to the Response Assessment in Pediatric Neuro-Oncology (RAPNO) criteria [22].

Patients were stratified into two groups based on Tanner stage: those in the early or prepubertal group (Tanner stage ≤ 3) and those in the advanced pubertal group (Tanner stage > 3). Precocious puberty was defined as the onset of secondary sexual characteristics before age 8 years old in females and 9 years old in males, confirmed by both hormonal assays and clinical criteria.

The primary endpoints of the study were the timing of tumor onset in relation to pubertal development, assessed using Tanner staging, and progression-free survival (PFS), defined as the interval from diagnosis to radiologically confirmed progression according to RAPNO criteria or death from any cause, with censoring at the date of the last evaluable MRI. These endpoints were selected to characterize the temporal relationship between pubertal maturation and tumor behavior. The exploratory endpoint was the effect of hormone-suppressive therapy with gonadotropin-releasing hormone (GnRH) analogues on PFS in patients with central precocious puberty, in order to explore the potential modulatory role of endocrine interventions on tumor dynamics during early pubertal development.

Statistics

Descriptive statistics were used to summarize demographic and clinical characteristics. Continuous variables were expressed as median and range, while categorical variables were presented as counts and percentages. Comparisons between groups were performed using the chi-square test or Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables. Kaplan-Meier survival analysis was conducted to estimate progression-free survival (PFS), and differences between groups were assessed using the log-rank test. Multivariate Cox proportional hazards regression models were applied to identify independent predictors of tumor progression, adjusting for potential confounders such as age, sex, tumor location, and treatment modality. Statistical significance was set at $p < 0.05$, and all analyses were performed using SPSS software version 27.0 (IBM Corp., Armonk, NY, USA).

Results

Cohort characteristics and tumor distribution

The study cohort consisted of 301 pediatric patients with radiologically confirmed low-grade gliomas (WHO grade 1 or 2); among them, 2 patients did not have a histological diagnosis due to the high risk associated with biopsy. nThe median age at diagnosis was 8.4 years, with a range from 1.2 months to 18 years. The population included 181 males (60%) and 120 females (40%). Tumor location was heterogeneous across the cohort: the cerebellum was the most commonly affected site (35%), followed by the cerebral hemispheres (32%), the optic pathway and hypothalamic region (19%), the brainstem (10%), and other less frequent locations (4%). Histopathological analysis identified pilocytic astrocytoma as the most prevalent histology, accounting for 55% of cases, followed by ganglioglioma (25%) and other low-grade gliomas (20%). Molecular profiling was available for 160 patients (53%). Among these, BRAF mutations were detected in 40% of cases, KIAA–BRAF fusions in 35%, and other less frequent alterations in the remaining 25%, reflecting the molecular heterogeneity of pediatric low-grade gliomas

Pubertal development and precocious puberty

At diagnosis or during follow-up, 112 of 301 patients (37%) exhibited advanced pubertal development, defined as Tanner stage greater than 3. Among these patients, 94 (82%) had physiological puberty, whereas 18 (6% of the whole cohort) met both clinical and hormonal criteria for central

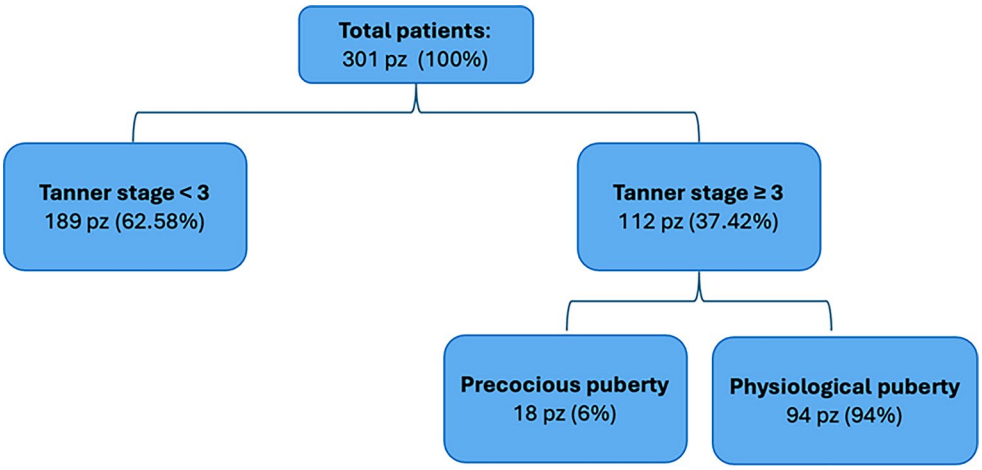


Fig. 1 Distribution of patients according to pubertal stage (Tanner stage < 3 vs > 3) at the time of diagnosis or progression of pLGGs

Table 1 Clinical, histopathologic, molecular, and treatment characteristics of patients with central precocious puberty (CPP)

Characteristic	Value
Number of patients	18
Sex	Female, 12; Male, 6
Tumor location	Diencephalic region: 17; Thalamus: 1
Histopathology	Pilocytic astrocytoma: 14 (78%); Ganglioglioma: 2 (11%); Not available (no biopsy): 2 (11%)
WHO grade	Grade 1 in all cases with available histology
Molecular profiling available	11 patients
BRAF mutation	5
KIAA1549–BRAF fusion	6
NF1	None
Surgical approach	Biopsy: 10; STR: 6; No biopsy: 2
GnRH analogue therapy	13 patients
Concomitant chemotherapy (LGG2004)	4
Concomitant mTOR inhibitor	2
Concomitant BRAFV600-targeted therapy	1
No concomitant systemic therapy	6
CPP patients without GnRH analogue therapy	5 patients
BRAFV600-targeted therapy	1
MEK inhibitor	2
mTOR inhibitor	1
Chemotherapy (LGG2004)	2

precocious puberty (CPP) (Fig. 1). Ten patients (55%) presented with signs of CPP before or at the time of tumor diagnosis, whereas the remaining eight patients (45%) developed CPP during the course of tumor progression. All patients with CPP had tumors involving the diencephalic region, with the exception of one patient with a thalamic lesion, supporting a potential anatomical and mechanistic association between tumor location and disruption of the hypothalamic–pituitary–gonadal axis (Table 1). Among patients with CPP, histopathologic evaluation identified pilocytic astrocytoma as the most common tumor subtype (14 patients, 78%), followed by ganglioglioma (2 patients, 11%). In two patients, histologic classification was unavailable because tumor biopsy was not performed owing to a high anticipated risk of postoperative neurologic sequelae. Molecular profiling was available for 11 patients and revealed BRAF mutations in 5 cases and KIAA1549–BRAF fusions in 6 cases; molecular data were not available for the remaining patients. None of the patients with CPP had a diagnosis of neurofibromatosis type 1 (NF1). Regarding surgical management, 10 patients underwent tumor biopsy and 6 underwent subtotal resection; in 2 patients, biopsy was not performed because of an anticipated high risk of surgical morbidity. Among the 13 patients with CPP who were treated with GnRH analogue therapy, 6 received concomitant chemotherapy according to the SIOP-LGG2004 protocol [5], 4 were treated with mTOR inhibitors, and 2 received targeted therapy for a BRAFV600 mutation; only one patient did not receive any concomitant

systemic antitumor therapy. In the untreated control group, 1 patient received BRAFV600-targeted therapy, 1 received MEK inhibitors, 1 received an mTOR inhibitor, and 2 were treated according to the SIOP-LGG2004 protocol [5]. Among the 18 patients with CPP, 5 did not receive GnRH analogue therapy because their age at CPP onset was borderline (between 7 and 8 years), and the endocrine management strategy favored clinical observation rather than hormonal suppression.

Effect of GnRH analogue on PFS

Among patients diagnosed with pLGG at or before 8 years of age, progression-free survival (PFS) was compared between two groups: 13 patients with central precocious puberty (CPP) who received a gonadotropin-releasing hormone (GnRH) analogue and 24 age-matched control patients with hypothalamic–optic pathway gliomas who did not develop CPP and did not receive GnRH analogue therapy. In the overall comparison, patients treated with a GnRH analogue showed a trend toward longer PFS compared with untreated controls; however, this difference did not reach statistical significance ($p=0.10$). At 36 months, PFS was 59.9% (95% confidence interval [CI], 39.0–92.0) in the GnRH-treated group and 91.7% (95% CI, 77.3–100) in the untreated control group (Fig. 2). When the analysis was restricted to patients with CPP, the association between GnRH analogue therapy and PFS became more pronounced. Within this subgroup, comparison between treated ($n=13$) and untreated ($n=5$) patients with CPP demonstrated a statistically significant difference favoring those who received GnRH analogue therapy ($p=0.00038$). At 30 months, PFS was 84.0% (95% CI, 60.0–97.0) in the treated cohort compared with 25.0% (95% CI, 3.0–56.0) among untreated patients. This difference was maintained at 60 months, with PFS rates of 78.0% (95% CI, 51.0–92.0) in treated patients and 25.0% (95% CI, 3.0–56.0) in untreated patients (Fig. 2) and (Fig. 3).

Treatment timeline and hormonal monitoring

The analysis of treatment timelines in patients with CPP who received GnRH analogues offers further insights into the potential relationship between hormonal modulation and tumor behavior (Table 2). Among the 13 treated patients, 2 (15.4%) experienced disease progression while still on GnRH analogue therapy (Fig. 4); these cases were characterized by biologically aggressive tumors that required multiple subsequent lines of treatment. Notably, the best radiologic response during GnRH analogue treatment was stable disease in all patients, except for one who achieved a partial response. An additional 4 patients (30.8%) showed tumor progression after discontinuation of the GnRH analogue. 3 out of these 4 patients (75%) exhibited pubertal reactivation following treatment withdrawal, and all three developed disease progression within one year of stopping therapy. This temporal association between the resumption of pubertal activity and tumor progression may suggest a potential link between hormonal fluctuations and disease dynamics. Hormonal parameters, summarized in Table 1, further support these observations by documenting changes in endocrine profiles before and after GnRH analogue therapy. These data reinforce the hypothesis that modulation of the hypothalamic–pituitary–gonadal axis may influence the

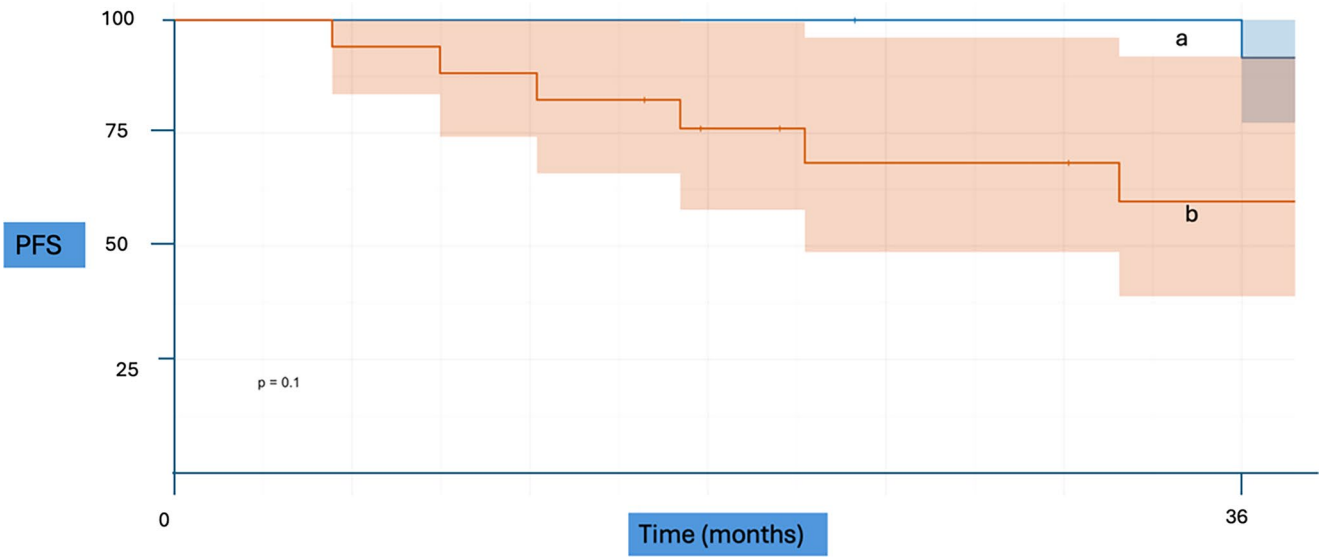
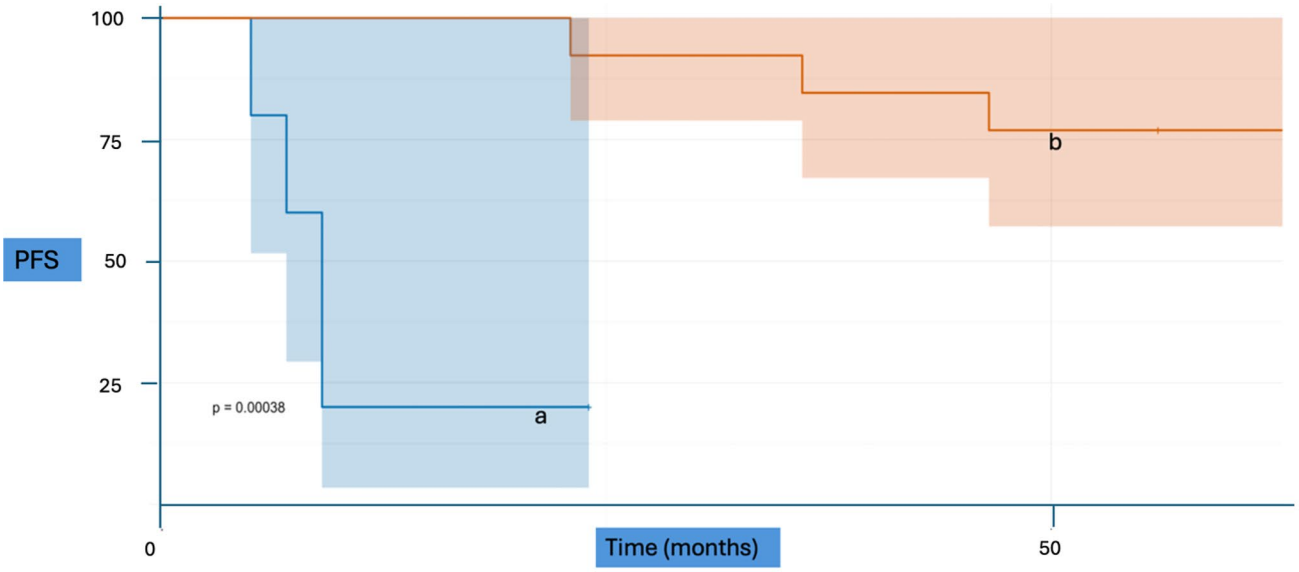


Fig. 2 Kaplan–Meier curve of progression-free survival (PFS) in children ≤ 8 years old at diagnosis or progression. Group a ($n=24$) includes patients with precocious puberty treated with GnRH analogues, while group B ($n=13$) includes patients with optic-pathway tumors without precocious puberty



Number at risk	0	24	48	72	96
Untreated (A)	5	1	0	0	0
GnRH (B)	13	12	9	5	3

Fig. 3 Kaplan–Meier curves showing progression-free survival (PFS) in children with central precocious puberty (CPP). Group a ($n=5$) includes untreated patients, while group B ($n=13$) includes patients treated with GnRH analogues

biological behavior of pediatric low-grade gliomas, particularly in cases involving the hypothalamic region.

Discussion

pLGGs are the most common CNS in the pediatric population. Although their course is generally indolent, these tumors can cause significant chronic morbidity, especially when their anatomical location prevents complete resection [3] and their progression contributes to the development of long-term neurological and endocrine sequelae [7]. In this context, the pediatric and adolescent age group introduces an additional layer of complexity: puberty. Specifically, among pediatric patients and adolescents and young adults (AYA) with pLGGs who experience either normal or precocious puberty, a period characterized by profound hormonal changes the interaction between endocrine maturation and tumor biology becomes critically important [9]. Therefore, understanding the role of sex hormones in tumor dynamics is essential to improve clinical outcomes and develop increasingly personalized treatment approaches.

Several studies have highlighted how estrogen and progesterone may modulate tumor behavior in various types of brain neoplasms, including gliomas, meningiomas, and chondromas [15]. The hormonal sensitivity of meningiomas is particularly well established: approximately 70% express progesterone receptors and 30% express estrogen receptors [12]. These receptors not only influence tumor growth which may accelerate during pregnancy or the menstrual cycle but also serve as prognostic markers, with PR expression being associated with a lower risk of recurrence [18]. Similarly, PR (particularly the PR-β isoform) have been identified in gliomas, with expression levels increasing with tumor histologic grade, suggesting a potential role in tumor progression. ARs are also overexpressed in gliomas, particularly in higher-grade tumors, and their expression is associated with worse prognosis in pLGGs, underscoring a potential role of AR in tumor growth and progression [13].

Supporting these findings, clinical cases have reported spontaneous or partial regression of pLGGs in patients undergoing pharmacological pubertal suppression for central precocious puberty. For instance, Kang et al. described regression of a pontine lesion following administration

Table 2 Hormonal profiles of patients with CPP treated with GnRH

Patient ID	Sex	Age at Diagnosis (yrs)	Tumor Location	Concomitant systemic treatment with triptorelin	Age Start triptorelin (yrs)	Age End Triptorelin (yrs)	Pre-treatment Hormones	Post-treatment Hormones	Hormones 1 Year After Discontinuation	Age at Progression (yrs)
P1	M	5	Thalamus	no	5	11	FSH 6, LH 10	FSH 0.6, LH 0.7	FSH 10, LH 5	12
P2	M	6	Diencephalon and optic pathways	SIOP-LGG2004	7	11	FSH 5.6, LH 18	FSH 0.6, LH 1.1	FSH 0.6, LH 2	-
P3	F	3	Diencephalon and optic pathways	SIOP-LGG2004	5	11	FSH 12.6, LH 2	FSH 1, LH 0.2	FSH 5, LH 0.2	9
P4	F	7	Diencephalon and optic pathways	imTOR	7	11	FSH 10, LH 7	FSH 1, LH 0.2	FSH 1.6, LH 0.6	-
P5	F	5	Diencephalon and optic pathways	SIOP-LGG2004	7	12	FSH 7.5, LH 7.1	FSH 2, LH 0.2	FSH 2, LH 3	-
P6	M	5	Diencephalon and optic pathways	imTOR	5	11	FSH 12, LH 4	FSH 0.2, LH 0.3	FSH 2, LH 8	-
P7	M	8	Diencephalon and optic pathways	iBRAFV600	8	11	FSH 5, LH 12	FSH 1, LH 0.2	FSH 1, LH 0.2	-
P8	M	5	Diencephalon and optic pathways	imTOR	7	On going	FSH 4.9, LH 2	FSH 0.6, LH 0.3	FSH 0.6, LH 0.3	-
P9	F	1	Diencephalon and optic pathways	SIOP-LGG2004	6	11	FSH 5.6, LH 6.5	FSH 0.6, LH 0.7	FSH 10, LH 12	12
P10	F	2	Diencephalon and optic pathways	imTOR	5	11	FSH 6, LH 5.5	FSH 0.9, LH 0.5	FSH 6.5, LH 9	12
P11	F	6	Diencephalon and optic pathways	SIOP-LGG2004	6	11	FSH 30, LH 79	FSH 2, LH 0.3	FSH 1, LH 0.3	-
P12	F	2	Diencephalon and optic pathways	iBRAFV600	4	10	FSH 4.9, LH 2	FSH 0.3, LH 0.3	FSH 0.3, LH 0.3	11
P13	M	3	Diencephalon and optic pathways	SIOP-LGG2004	5	8	FSH 7, LH 3	FSH 0.3, LH 0.3	FSH 0.3, LH 0.3	7

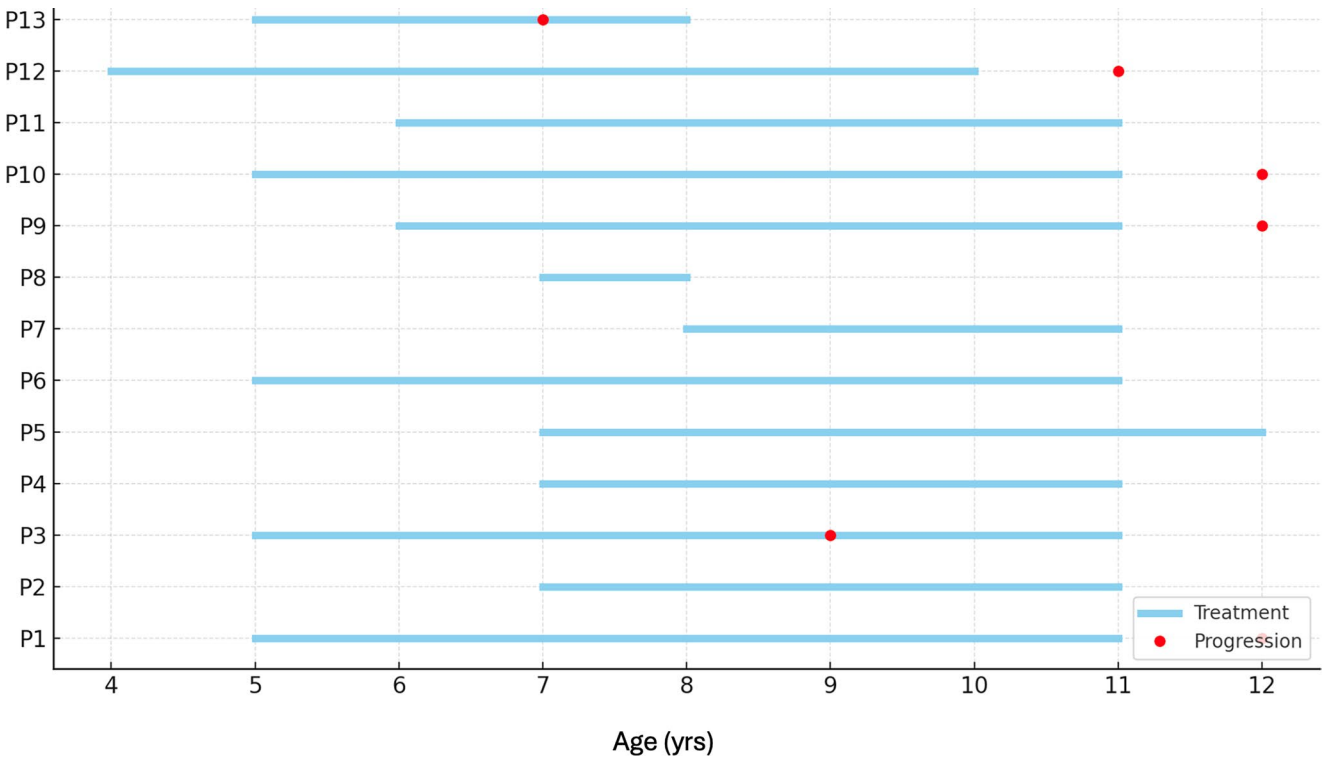


Fig. 4 Treatment timeline with GnRH in patients with hypothalamic-optic pathway glioma. Each horizontal row corresponds to a patient. Horizontal bars indicate the duration of treatment, with the red symbol indicating the event of disease progression

of a GnRH analogue [16], while another case reported greater than 50% tumor shrinkage after three years of GnRH analogue therapy in a 2-year-old girl, suggesting a potential anti-proliferative effect of hormonal suppression in selected subgroups [17]. Pregnancy, characterized by marked increases in estrogen and progesterone levels, also offers a natural model for studying the impact of sex hormones on tumor growth. Several case series have described accelerated glioma progression during pregnancy, with early clinical deterioration and increased seizure frequency, particularly in low-grade gliomas [18]. Peeters and Pallud documented tumor growth acceleration in 87% of pregnancies in women with gliomas, highlighting a potential direct role of endocrine changes in influencing tumor behavior [19, 20]. Against this background, our retrospective study draws attention to the previously underexplored role of pubertal development and hormonal modulation in pLGGs. We observed that a substantial proportion of patients (37%) reached an advanced pubertal stage (Tanner stage > 3) either at diagnosis or during disease progression, and that 6% developed CPP. Nearly all patients with CPP had tumors involving the diencephalic region, with only one case arising in the thalamus. This observation is consistent with prior reports indicating that tumors affecting the hypothalamic–pituitary axis can disrupt gonadotropin regulation and precipitate early pubertal onset [8, 9]. Importantly, beyond a purely mechanical effect, our findings support the hypothesis that the hormonal milieu particularly sex hormones may actively influence tumor growth and behavior.

Experimental data from preclinical studies further support this hypothesis and provide insights into the complex role of sex hormone receptors in glioma biology. Estrogen receptors, including ERα, ERβ, and the G protein-coupled estrogen receptor 1 (GPER1), along with androgen receptors (AR) and progesterone receptors (PR), are variably expressed in glial tumors [14, 23, 24]. Among these, ERα and GPER1 are capable of activating important oncogenic pathways such as the MAPK/ERK and PI3K/AKT/mTOR cascades, which are known to promote cell proliferation, survival, and migration [2]. Activation of these pathways can lead to increased tumor growth and invasiveness.

In contrast, ERβ appears to play an opposing role by exerting tumor-suppressive effects, often through pro-apoptotic mechanisms and inhibition of proliferative signals. The expression levels and relative activities of these receptor subtypes create a complex hormonal environment that can influence tumor behavior [14]. During puberty, when hormone levels rise dramatically, this balance can be disrupted, particularly if some receptors are over- or under-expressed. Such receptor imbalance may foster cell proliferation, angiogenesis, and remodeling of the tumor microenvironment [25]. This phenomenon is especially relevant in pediatric low-grade gliomas (pLGGs), where MAPK pathway activation already represents a central oncogenic driver [2]. The crosstalk between hormone receptor-mediated signaling and MAPK pathway activation may synergistically amplify tumor progression. Additionally, the PI3K/AKT/mTOR pathway, also modulated by these receptors, plays a crucial role in cell growth and metabolism and may further exacerbate tumor aggressiveness when dysregulated [7]. Furthermore, although androgen receptors are less studied in glial tumors, they may contribute to tumor biology by interacting with similar signaling pathways or influencing gene expression profiles involved in cell cycle regulation [13]. The interaction between estrogenic and androgenic signaling pathways creates a complex network capable of modulating tumor dynamics, particularly during periods of intense hormonal activity such as puberty. These preclinical data therefore highlight the importance of considering hormone receptor expression profiles and their downstream signaling effects in the study of glioma physiology and the development of therapeutic approaches.

Importantly, our findings suggest that hormonal suppression with GnRH analogues may potentially influence tumor behavior in pediatric patients, although these observations requires confirmation in larger studies. Among children with CPP, those treated with GnRH analogues experienced significantly longer progression-free survival than untreated patients. This benefit persisted at long-term follow-up (60 months), and the temporal association between pubertal reactivation after treatment discontinuation and subsequent tumor progression further supports the biological plausibility of this relationship. These observations raise important mechanistic and therapeutic questions. Does hormonal suppression primarily delay tumor progression, or can it induce more durable changes in tumor biology? Could endocrine modulation be integrated into multimodal treatment strategies, particularly for inoperable tumors or those that progress despite conventional therapies? Although hormonal blockade is well established in conditions such as CPP and hormone-sensitive malignancies, including breast and prostate cancer, its role in pediatric neuro-oncology remains largely unexplored [26]. The relationship between pubertal timing and tumor onset also warrants attention. In several patients, CPP developed before or concurrently with tumor diagnosis, suggesting a potential bidirectional interaction: hypothalamic tumors may precipitate early puberty, while pubertal hormonal signals may, in turn, accelerate tumor onset or progression in hormone-responsive tissues. This concept parallels observations in adult glioma cohorts, in which pregnancy and exposure to exogenous hormones have been associated with accelerated tumor growth [18]. However, the pediatric context is distinct, given the plasticity of neuroendocrine development and the prolonged therapeutic

trajectories typical of pLGGs. Collectively, these findings raise the possibility that endocrine modulation could be incorporated into the multimodal management of selected pLGGs, particularly in patients with hypothalamic–optic pathway tumors and potentially hormone-responsive disease. Whether GnRH analogue therapy primarily delays progression or induces more sustained biologic changes remains to be determined. Nevertheless, the favorable safety profile of GnRH analogues and their established use in CPP suggest that, in carefully selected patients, hormonal suppression may represent a low-toxicity adjunct to chemotherapy, targeted therapy, or radiotherapy.

Limitations

These findings should be interpreted in the context of several limitations. First, the retrospective nature of the study precludes causal inference and introduces potential selection bias. Variability in treatment timing and duration of follow-up may have further influenced outcome measures. In addition, the relatively small number of patients with central precocious puberty limited the statistical power of subgroup analyses and restricted the feasibility of comprehensive multivariable modeling.

Moreover, hormone receptor expression was not systematically evaluated in tumor specimens, preventing direct correlations between endocrine signaling pathways and clinical outcomes. As a result, the biological mechanisms underlying the observed clinical associations could not be directly interrogated in this cohort. Despite these limitations, this study provides an initial clinical framework supporting pubertal development as a biologically relevant factor in pediatric low-grade gliomas. Future prospective studies incorporating standardized longitudinal endocrine assessments, integrated molecular profiling—including systematic evaluation of hormone receptor expression—and complementary preclinical approaches such as patient-derived organoid models will be essential to validate these findings and to identify patient subgroups most likely to benefit from endocrine-modulating therapeutic strategies

Conclusions

This study suggests that puberty may not represent merely a physiological background in pediatric neuro-oncology but may also contribute to modulating the biological behavior of pediatric low-grade gliomas (pLGGs). In our cohort, among patients with central precocious puberty, advanced pubertal development was frequently associated with tumors involving the hypothalamic–optic pathway. Moreover, in our cohort, hormonal suppression with GnRH analogues in patients with central precocious puberty was associated with a possible trend toward improved progression-free survival (PFS) compared with untreated patients. These observations suggest that systematic monitoring of pubertal development, together with integrated endocrine evaluation in patients with tumors of the hypothalamic–optic region, may contribute to a better clinical characterization of these patients and potentially inform more personalized management strategies.

However, larger prospective studies and mechanistic investigations will be necessary to clarify the potential role of pubertal hormonal variations and endocrine modulation in the biology of pLGGs and to determine whether such interventions may have clinical implications within precision medicine approaches in pediatric neuro-oncology.

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Author contributions Conceptualization: AC, AM Data curation: FDA, SR, GM, GDB, VC Formal analysis: FDA, AC, AM Investigation: FDA, SR, AC, GM, GDB, VC Methodology: AC, AM, FL Project administration: AC Visualization: FDA, AC, AM, GSC, CD, AR, FL Writing - original draft: FDA, AC Writing - review\& editing: AM, AC, FL (FDA $=$ Federica D'Antonio; $\mathrm{SR}=$ Sabrina Rossi; $\mathrm{AC}=$ Antonella Cacchione; $\mathrm{AR}=$ Andrea Carai; GSC $=$ Giovanna S. Colafati; $\mathrm{CD}=$ Claudia D'Orazio; $\mathrm{GM}=$ Giacomina Megaro; $\mathrm{GDB}=$ Giada Del Baldo; VC = Veronica Capelli; FL = Franco Locatelli; AM = Angela Mastronuzzi).

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Data availability The datasets generated and/or analyzed during the current study are not publicly available due to patient confidentiality and data-sharing restrictions between institutions. Anonymized data may be made available from the corresponding author upon reasonable request, subject to approval by the relevant Ethics Committees and data use agreements.

Declarations

Ethics and consent to participate The study was conducted in accordance with the Declaration of Helsinki and was approved by the local Ethics Committee. Due to the retrospective nature of the study, informed consent was waived.

Competing interests The authors declare no competing interests.

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