Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/6xwc7p91

# PEDIATRIC LOW-GRADE GLIOMAS: A FINE BALANCE BETWEEN TREATMENT OPTIONS, TIMING OF THERAPY, SYMPTOM MANAGEMENT AND QUALITY OF LIFE: EXPERIENCE FROM A TERTIARY CARE CENTRE IN LMIC

**Syeda Tehreem Zahra Gillani[1], Najma Shaheen[2*], Aruba Nawaz Khattak[3], Muhammad Omer Khan Tareen[4]**

[1]Fellow Pediatric Hematology and Oncology, Shaukat Khanum Hospital Lahore, Pakistan
[2*]Consultant Pediatric Oncologist, Shaukat Khanum Hospital Lahore, Pakistan
[3]Fellow Body Imaging, Shaukat Khanum Hospital Lahore, Pakistan
[4]Medical Officer, Shaukat Khanum Hospital Lahore, Pakistan

***Corresponding author:** Najma Shaheen
*Email: Tehreem.zahragillani@gmail.com

## ABSTRACT

Pediatric low-grade gliomas (LGGs) are the most frequently observed brain tumors in the pediatric age groups. Diagnosing LGGs generally needs a combination of imaging and histopathological studies following the biopsy. As LGGs are generally benign, their location may contribute to major complications, especially when located near critical brain structures. Treatment in pediatric LGGs usually invovles surgery, chemotherapy, and occasionally radiation therapy, and the choice is based on the location of the tumor, along with the symptoms and overall clincial profiling of the child. This case reports presents a 5-year-old boy who was havinga BRAF-positive pilocytic astrocytoma, and developed progressive symptoms. Initial surgery could only have achieved partial resection due to the tumor's deep and awkward location in the suprasellar and basal ganglia areas. The children was advised to undergo a 70-week course of vinblastine chemotherapy, which resulted in temporary stabilization of the initial symptoms. However, the disease progressed in the following period, requiring a 2nd line treatment with vincristine and carboplatin that resulted in only partial response. Subsequent interventions invovled palliative radiotherapy and the placement of an Ommaya reservoir to drain the cystic fluid, which yielded neurological improvements. This case report highlights the challenges of treating refractory pediatric LGGs, especially at a tertiary care center of a resource-limited setting.

**Keywords:** Chemotherapy, low-grade glioma, neurological deficit, surgery, tumor.

## INTRODUCTION

Pediatric low-grade gliomas (LGGs) are commonly occurring brain tumors in the pediatric age groups, constituting around 30% of all pediatric central nervous system (CNS) tumor cases.[1] LGGs generally originate from glial cells, that are considered essential for the support and protection of neurons in the brain.[2] LGGs are usually slow-growing with a favorable prognosis in vast majority of the cases. The clinical course of LGGs may vary significantly depending upon the location and size fo the tumor, along with the involvement of nearby structures. LGGs most frequently affect optic pathways, brainstem, and cerebellum,[3] while the diagnosis commonly requires the employment of

imaging and histopathological analysis after biopsy.[4] As LGGs are usually benign but their location can cause significant morbidity including neurological issues.[5] Treatment of LGGs involve surgery, chemotherapy, and radiation, based upon the tumor's details, clinical profile and the the presenting symptoms. LGGs have good surival rates but long-term outcomes can be influenced by treatment related side-effects.[6] The present data research is majorly focusing a deeper understanding of the molecular as well as the genetic aspects of LGGs which may lead the way for more targeted and less harmful treatment options.

## CASE REPORT

A 5-year-old boy from Afghanistan presented with chief complaints of loss of vision in the right eye and recurrent seizures. The child also exhibited symptoms of polyuria and polydipsia, was on follow up with endocrinology. His neurological symptoms and visual impairment had progressively worsened over the preceding months, raising significant concern. Pre-operative MRI scan revealed a lobulated, infiltrative mass in the supra sellar region. A deep seated tumor in basal ganglia and bilateral thalami posed a surgical challenge for gross total resection (figure-1). The children had underwent right craniotomy and tumor resection in Afghanistan but no complete resection was achieved as expected due to location of the tumor. The histopathological examination was consistent with LGG favoring pilocytic astrocytoma WHO grade 1 BRAF mutation positive .

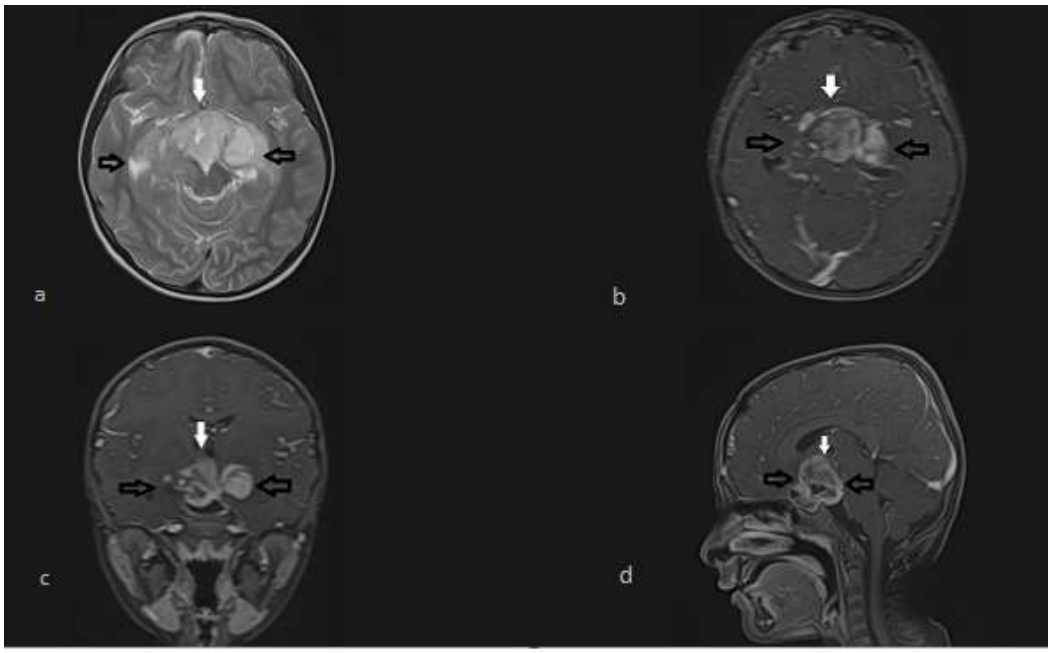


**Figure 1: (a,b,c,d) Heterogeneously enhancing predominantly solid mass with epicenter in suprasellar region with involvement of medial temporal lobes and basal ganglia bilaterally (black arrows). Extension into quadrigeminal cistern (white arrows). No hydrocephalus.**

Concurrently, child experienced significant vision loss, with no vision in the right eye and an inability to localize objects with the left eye, however no cerebellar signs were observed with rest of the neurological status intact. Given the inoperable nature of the tumor, the patient was initiated on a weekly chemotherapy regimen with vinblastine, following the National protocol for low-grade glioma.[7] Completing the 70 weeks of weekly vinblastine, cinical neurological status improved in terms that the child was able to walk independently and was able to localize objects. The disease remained stable on follow-up surveillance scans for 6 months, and progressed eventually at local site and developed solid cystic mass along both basal ganglia with increase in hydrocephalus ( figure 2).

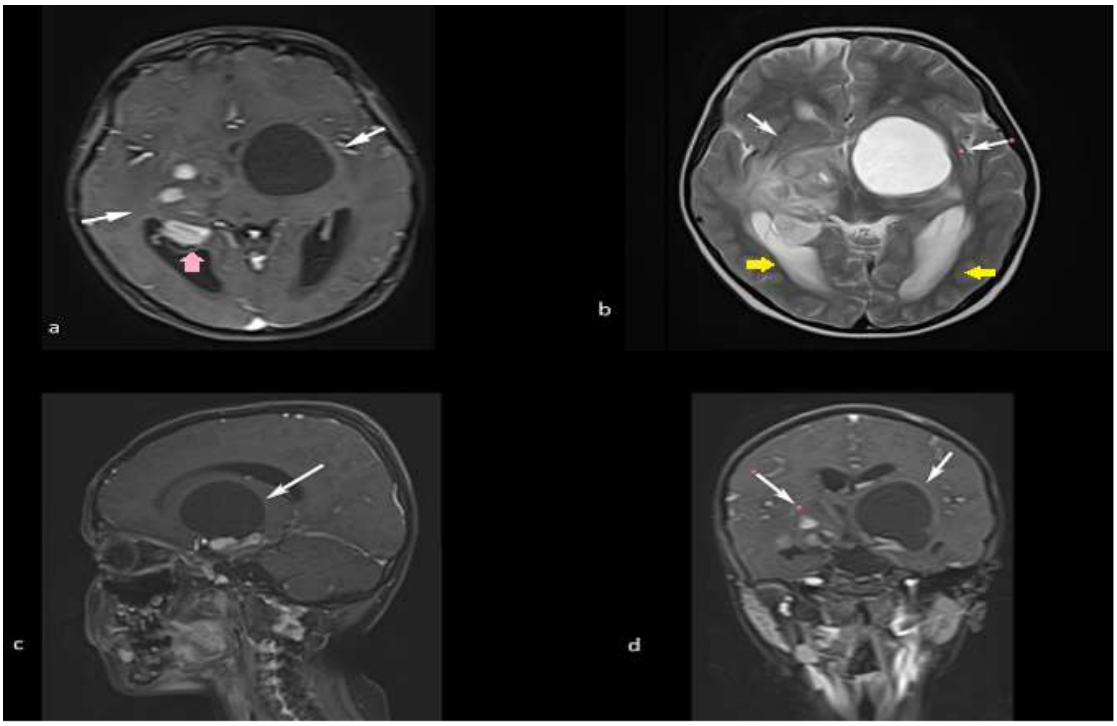


**Figure 2: (A, B, C, D) : Marginal interval increase in size of lesion centered in suprasellar region extending to medial temporal lobes and basal ganglia. (A) Intraventricular extension into right occipital horn. (B) Interval development of hydrocephalus.**

Clinical status deteriorated as the child developed generalized hypertonia, abnormal movements, cranial nerve signs, persistent vomiting and headache, complete loss of vision, no perception of light, incomprehensible speech, constricted pupil and depressed conscious level. In response to the disease progression, a 2nd line chemotherapy regimen, consisting of six cycles of vincristine and carboplatin, was initiated for 6 months in accordance with National guidelines for low-grade glioma.[7] There was an interval partial treatment response on this line, however, eventually patient progressed on this line of chemotherapy as well. (figure 3)

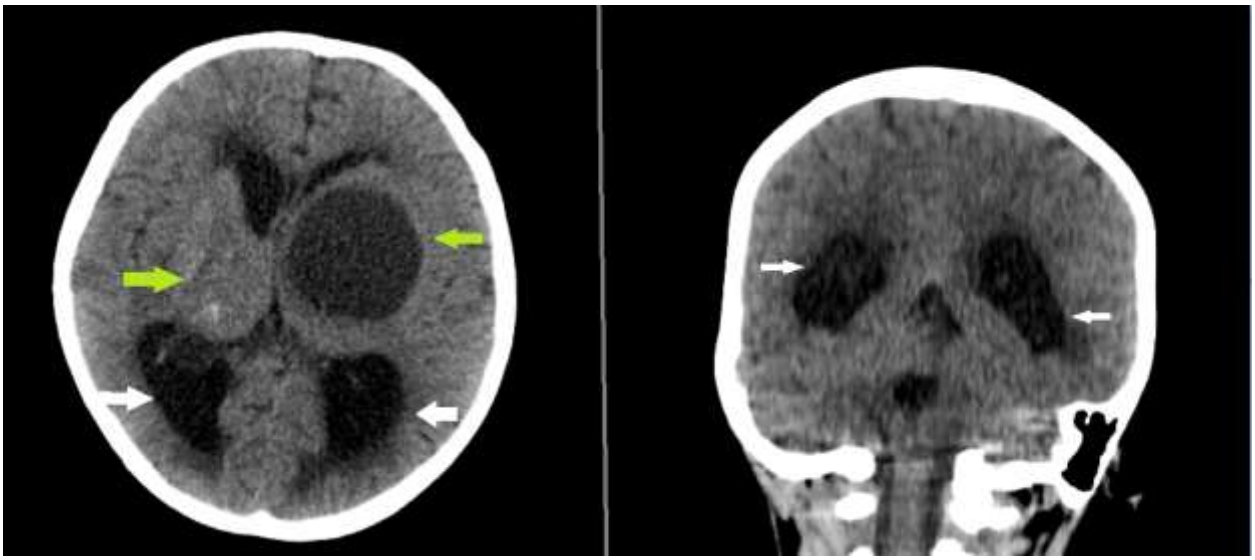

**Figure 3: CT brain axial image with coronal reformat showing re-demonstration of large tumor centered over bilateral basal ganglia. Interval increase in the size of cystic component of the tumor involving left basal ganglia and internal calcifications in part of lesion centered on right basal ganglia (green arrows). Interval increase in hydrocephalus (white arrows).**

Patient was discussed in multiple National Neuro oncology multidisciplinary teams (MDTs) for radiation plan, as well as, for any 3rd line chemotherapy. As the sites were not Biopsiable, so deffered 3rd line chemotherapy . A course of steroids was initiated which did not improve the neurological status. Children was given 20gy/5fractions in palliative intent. Neurosurgical intervention was done in the form of Neuro navigation assisted left basal ganglia Omaya Reservoir placement for cyst deflation and drainage (figure 4). Patient responded well after the intervention and neurological status improved in means of improved conscious status , decreased hypertonia and rigidity, comprehensive speech and alert mental status.

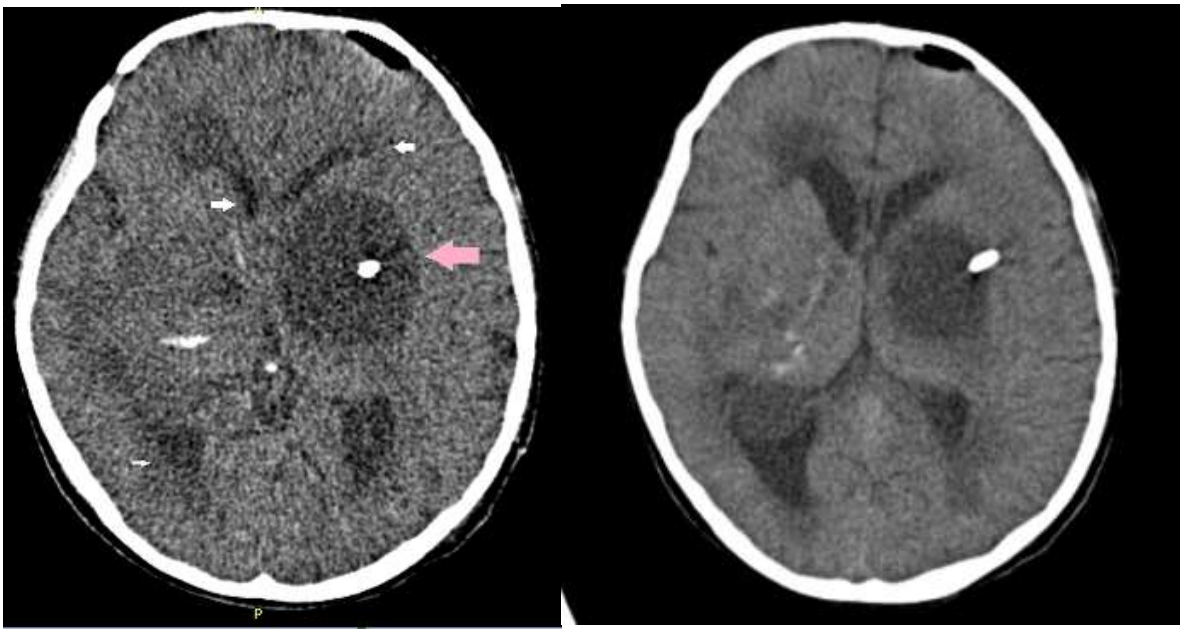

**Figure 4 : Interval placement of ommaya reservoir in the cystic component of left thalamic solid/cystic mass (pink arrow) with resultant decrease in size. Iatrogenic left frontal pneumocephalus (blue curved arrows). Peristsent right hydrocephalus (orange arrows). Left lateral ventricle further decompressed.**

## DISCUSSION

Pediatric LGGs are generally slow-growing and carry a low likelihood of turning malignant, with impressive survival rates—5-year overall survival (OS) approaches 97%, while 10- and 20-year OS hover around 90%.[8,9] However, progression-free survival (PFS) is often lower, particularly in cases with residual tumors, where PFS rates of 45%-65% have been reported.[10] These tumors frequently arise in challenging areas like the brainstem and suprasellar region, and both their location and the treatment can lead to substantial morbidity, including vision impairment, functional limitations, hormonal imbalances, motor and cognitive disabilities, and decreased quality of life.[11,12] Treatment strategies focus on sustained tumor control with minimal impact on these functions and overall quality of life. When feasible, gross total resection is preferred. For tumors that are not fully resectable or show progression, additional therapies—such as chemotherapy, targeted treatments, or radiation—are often employed.[13,14] Advancements in molecular diagnostics have revealed that most pediatric LGGs exhibit activation of the RAS/MAPK signaling pathway, making targeted treatments a promising avenue.[11,15] Early research indicates that loss of heterozygosity (LOH) in 1p and 19q holds potential, though long-term side effects remain unclear. Should ongoing trials demonstrate both efficacy and safety, targeted treatments may soon play a central role in pediatric LGG management. Notably, the BRAF gene, a key part of the Raf family of serine/threonine kinases, is a significant downstream target in the MAPK pathway and contributes to oncogenic processes, further supporting the rationale for targeted therapies in this setting.[16]

The present case underscores the complexities inherent in managing pediatric LGGs, particularly those harboring BRAF mutations and located in surgically challenging regions. The BRAF V600E mutation is implicated in the activation of the MAPK/ERK signaling pathway, contributing to tumorigenesis. Targeted therapies have shown promise in treating BRAF-mutated pediatric LGGs but the access to these relatively newer therapies is limited in certain regions, marking vast unqualities in the global healthcare. This care report highlighted challenges in managing pediatric LGGs with limited resources and underscores the importance of a multidisciplinary approach. It requires collaboration among neurosurgeons, oncologists, radiologists, and endocrinologists that can result in optimizing clinical outcomes. There is also a need for the accessible molecular diagnostics that can help in identification of actionable mutations, helping in choosing the employment of targeted therapies.

In conclusion, this case illustrates the intricate challenges in treating pediatric LGGs, particularly those with unfavorable locations and genetic mutations. It emphasizes the necessity for comprehensive, multidisciplinary care and the importance of advancing access to molecular diagnostics and targeted therapies to improve outcomes for pediatric patients worldwide.

## PATIENT'S CONSENT:

Informed consent was obtained from the parent of the child.

## COMPETING INTEREST:

The authors declared no competing interest

## SPONSORSHIP OR FUNDING:

None

## AUTHOR'S CONTRIBUTION

**STZG:** Data collection, synthesis, drafting, responsible for data, approved for publication
**NS:** Conception, design, supervision, proof reading, critical revision, approved for publication
**ANK:** Data collection, synthesis, responsible for data, proof reading, approved for publication

## REFERENCES

1. Bale TA, Rosenblum MK. The 2021 WHO Classification of Tumors of the Central Nervous System: An update on pediatric low-grade gliomas and glioneuronal tumors. Brain Pathol. 2022 Jul;32(4):e13060. doi: 10.1111/bpa.13060
2. Goebel AM, Gnekow AK, Kandels D, Witt O, Schmidt R, Hernáiz DP. Natural History of Pediatric Low-Grade Glioma Disease - First Multi-State Model Analysis. J Cancer 2019; 10(25):6314-26. doi:10.7150/jca.33463
3. Sadighi ZS, Curtis E, Zabrowksi J, Billups C, Gajjar A, Khan R, et al. Neurologic impairments from pediatric low-grade glioma by tumor location and timing of diagnosis. Pediatr Blood Cancer. 2018 Aug;65(8):e27063. doi: 10.1002/pbc.27063
4. Funakoshi Y, Hata N, Kuga D, Hatae R, Sangatsuda Y, Fujioka Y, et al. Pediatric Glioma: An Update of Diagnosis, Biology, and Treatment. Cancers (Basel). 2021 Feb 12;13(4):758. doi: 10.3390/cancers13040758
5. Hauser P. Classification and Treatment of Pediatric Gliomas in the Molecular Era. Children (Basel). 2021 Aug 27;8(9):739. doi: 10.3390/children8090739
6. Traunwieser T, Kandels D, Pauls F, Pietsch T, Warmuth-Metz M, Bison B, et al. Long-term cognitive deficits in pediatric low-grade glioma (LGG) survivors reflect pretreatment conditions-report from the German LGG studies. Neurooncol Adv. 2020 Aug 8;2(1):vdaa094. doi: 10.1093/noajnl/vdaa094

7. Pakistan National Guidelines for the diagnosis and management of Paediatric and adolescent LowGrade Glioma. 2021. Available at: https://pasno.org/wp-content/uploads/2023/01/LGG-Guidlines.pdf
8. Krishnatry R, Guerreiro Stucklin AS, Pole JD, Mistry M, Fried I, et al. Clinical and treatment factors determining long-term outcomes for adult survivors of childhood low-grade glioma: A population-based study. Cancer. 2016;122:1261–9. doi: 10.1002/cncr.29907
9. Bandopadhayay P, Bergthold G, London WB, Goumnerova LC, Morales La Madrid A, Marcus KJ, et al. Long-term outcome of 4,040 children diagnosed with pediatric low-grade gliomas: an analysis of the Surveillance Epidemiology and End Results (SEER) database. Pediatr Blood Cancer.2014;61:1173–9. doi: 10.1002/pbc.24958
10. Shaw EG, Wisoff JH. Prospective clinical trials of intracranial low-grade glioma in adults and children. Neuro Oncol. 2003;5:153–60. doi: 10.1215/S1152851702000601
11. Ryall S, Tabori U, Hawkins C. Pediatric low-grade glioma in the era of molecular diagnostics. Acta Neuropathol Commun. 2020;8:30. doi: 10.1186/s40478-020-00902-z
12. Wisoff JH, Sanford RA, Heier LA, Sposto R, Burger PC, Yates AJ, et al. Primary neurosurgery for pediatric low-grade gliomas: a prospective multi-institutional study from the Children's Oncology Group. Neurosurgery. 2011;68:1548–54. doi: 10.1227/NEU.0b013e318214a66e
13. de Blank P, Bandopadhayay P, Haas-Kogan D, Fouladi M, Fangusaro J. Management of pediatric low-grade glioma. Curr Opin Pediatr. 2019;31:21–7. doi: 10.1097/MOP.0000000000000717
14. Rosca L, Robert-Boire V, Delisle JF, Samson Y, Perreault S. Carboplatin and vincristine neurotoxicity in the treatment of pediatric low-grade gliomas. Pediatr Blood Cancer. 2018;65:e27351. doi: 10.1002/pbc.27351
15. Ryall S, Zapotocky M, Fukuoka K, Nobre L, Guerreiro Stucklin A, Bennett J, et al. Integrated molecular and clinical analysis of 1,000 pediatric low-grade gliomas. Cancer Cell. 2020;37:569–83.e5. doi: 10.1016/j.ccell.2020.03.011
16. Manoharan N, Liu KX, Mueller S, Haas-Kogan DA, Bandopadhayay P. Pediatric low-grade glioma: Targeted therapeutics and clinical trials in the molecular era. Neoplasia. 2023;36:100857. doi: 10.1016/j.neo.2022.100857