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**Recommended Citation**

Brossier, Nicole M; Strahle, Jennifer M; Cler, Samuel J; Wallendorf, Michael; and Gutmann, David H, "Children with supratentorial midline pilocytic astrocytomas exhibit multiple progressions and acquisition of neurologic deficits over time." Neuro-Oncology Advances. 4, 1. vdab187 (2022).  
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Children with supratentorial midline pilocytic astrocytomas exhibit multiple progressions and acquisition of neurologic deficits over time

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Pilocytic astrocytomas (PAs) are the most common brain tumors of childhood\(^1\) and can arise anywhere within the neuroaxis, including the posterior fossa (pf-PA), supratentorial midline (sm-PA; including optic pathway, hypothalamus, thalamus), supratentorial cortex (sc-PA), brainstem (bs-PA), and spinal cord (sp-PA). While tumor location (sm, bs) has been proposed as a prognostic factor associated with poor progression-free survival (PFS),\(^2\)\(^,\)\(^3\) this effect is abrogated when resection status (gross total resection [GTR], subtotal resection [STR]) is included.\(^2\)\(^,\)\(^4\) To determine whether tumor location has any value in predicting PA clinical outcome, we evaluated clinical outcomes of children with biopsy-proven PA treated at St. Louis Children's Hospital between 2003 and 2021 (n = 251). Subjects with a diagnosis of neurofibromatosis type 1 (NF1; n = 13) and those with discrepancies in their pathologic diagnosis (n = 11) or missing pertinent clinical data (n = 36) were excluded, leaving 191 total subjects for analysis. Consistent with prior reports,\(^5\) children with sc-PA were typically older at diagnosis than those with pf-PA. There were no differences in PA location incidence by sex,\(^1\) but individuals with sm-PA and bs-PA had higher rates of STR (Figure 1A) and reduced PFS (Figure 1B).\(^2\)\(^,\)\(^3\) Importantly, this difference in PFS was related to resection status, such that longer PFS was observed in sm-JPA and bs-JPA cases in which a GTR was achieved (Figure 1C).

To determine how differences in clinical course by brain location affected neurologic outcomes, we then quantified neurologic deficits at diagnosis, relapse, and last follow-up in subjects with STR PA. One point was awarded for the presence of each deficit at initial diagnosis, including unilateral facial weakness, dysphagia, dysarthria, unilateral upper extremity weakness, unilateral lower extremity weakness, vision loss, hearing loss, each endocrinopathy present, ataxia, mutism, seizures, and severe cognitive impairment. At follow-up, one point was added for worsening symptoms or new symptoms and removed for resolved symptoms. A half-point was removed for improving, but not resolved, neurologic signs/symptoms. Scores at follow-up were subtracted from scores at initial diagnosis to generate a curve over time, with each subject's score at diagnosis acting as an internal standard. As expected, there were qualitative differences in neurologic deficits by brain location, with vision loss and endocrinopathies more prevalent in sm-PA, and weakness and bulbar symptoms more prevalent in bs-PA. While the number of neurologic deficits did not differ by brain location at initial diagnosis (Figure 1G), children with sm-PA exhibited more neurologic deficits over time (Figure 1H), frequently due to worsening vision and the acquisition of new endocrinopathies or weakness. In contrast, subjects with bs-PA typically displayed deficits at initial presentation or in the immediate postoperative period that remained stable or improved over time.
Given that different driver mutations may also affect clinical prognosis in pediatric low-grade glioma (pLGG), we next determined whether mutations differed by brain location. Molecular testing data were available for 51 subjects (22 GTR, 29 STR), which included BRAF-fusion analysis by FISH (n = 51), BRAFV600E detection by immunohistochemistry (n = 50), and targeted tumor sequencing (n = 25; 14 pf-PA, 8 sm-PA, 3 bs-PA). Similar to prior reports, we found that subjects with sm-PA had more non-BRAF-fusion alterations identified (Figure 1I), including oncogenic mutations in BRAF (V600E, D594G), FGFR1, PTPN11, and other (KMT2C, CDH1) genes. Additionally, sm-PAs had a greater occurrence of multiple oncogenic mutations compared to pf-PAs (25% vs 10% of cases; Figure 1I), with secondary mutations in either PTPN11 or CDH1 identified in 75% of sm-JPAs with multiple mutations.

Taken together, we identified a subgroup of children with PA with a more aggressive clinical course, greater numbers of neurological deficits acquired over time, and an elevated prevalence of non-BRAF-fusion genetic alterations. By restricting our analysis to STR PA cases, we eliminated resection status as a confounding variable, and confirmed location as an independent prognostic factor. Similar to prior studies, the effect of location was eliminated for PA in which GTR could be achieved.

In our series, children with m-PA also displayed worsening neurological deficits over time, a finding not reported in prior studies. This discrepancy may be due to methodology, as our study included only subjects with PA,
excluded those with GTR, and removed individuals with NF1, who often develop sm-LGG with a more indolent course. The clinical course of sporadic sm-PA was more reminiscent of deep extensive tumors in children with NF1, which arise in younger subjects, require multiple treatments, and exhibit a shorter mean PFS. The higher rates of multiple progression, which correlates with increased neurologic morbidity, in young children with sporadic STR sm-PA suggests that treating neuro-oncologists may consider early intervention at first progression, rather than watch-and-wait strategies. These at-risk children may also benefit from earlier consideration of molecularly targeted therapy.

**Funding**

This work was supported by grants from Alex’s Lemonade Stand Foundation (18-12558) to N.M.B., Hyundai Hope on Wheels (DR-2019-672) to N.M.B., the National Institute of Child Health & Human Development (K12) to N.M.B., and a Research Program Award from the National Institute of Neurological Disorders and Stroke (1-R35-NS097211-01) to D.H.G.

**Conflict of interest statement.** The authors declare no relevant conflicts of interest.

**Authorship statement.** Conceptualization: N.M.B. and J.M.S.; Methodology: N.M.B.; Investigation: N.M.B., S.J.C., and J.M.S; Statistical analyses: N.M.B. and M.W.; Writing—original draft: N.M.B. and D.H.G.; Writing—review and editing: D.H.G.; Supervision: D.H.G.; Funding acquisition: N.M.B. and D.H.G.

**References**

1. Ostrom QT, de Blank PM, Kruchko C, et al. Alex’s Lemonade stand foundation infant and childhood primary brain and central nervous system tumors diagnosed in the United States in 2007–2011. Neuro Oncol. 2015;16(Suppl 10):x1–x36.

2. Fernandez C, Figarella-Branger D, Girard N, et al. Pilocytic astrocytomas in children: prognostic factors—a retrospective study of 80 cases. Neurosurgery. 2003;53(3):544–553; discussion 554-545.

3. Colin C, Padovani L, Chappé C, et al. Outcome analysis of childhood pilocytic astrocytomas: a retrospective study of 148 cases at a single institution. Neuropathol Appl Neurobiol. 2013;39(6):693–705.

4. Villanueva KG, Rea ND, Krieger MD. Novel surgical and radiologic risk factors for progression or recurrence of pediatric pilocytic astrocytoma. Pediatr Neurosurg. 2019;54(6):375–385.

5. Ryall S, Zapotocky M, Fukuda K, et al. Integrated molecular and clinical analysis of 1,000 pediatric low-grade gliomas. Cancer Cell. 2020;37(4):569–583.e5.

6. Zhang J, Wu G, Miller CP, et al.; St. Jude Children’s Research Hospital–Washington University Pediatric Cancer Genome Project. Whole-genome sequencing identifies genetic alterations in pediatric low-grade gliomas. Nat Genet. 2013;45(6):602–612.

7. Sadighi ZS, Curtis E, Zabrowski J, et al. Neurologic impairments from pediatric low-grade glioma by tumor location and timing of diagnosis. Pediatr Blood Cancer. 2018;65(8):e27063.

8. Listernick R, Charrow J, Greenwald M, Mets M. Natural history of optic pathway tumors in children with neurofibromatosis type 1: a longitudinal study. J Pediatr. 1994;125(1):63–66.

9. Listernick R, Darling C, Greenwald M, Strauss L, Charrow J. Optic pathway tumors in children: the effect of neurofibromatosis type 1 on clinical manifestations and natural history. J Pediatr. 1995;127(5):718–722.

10. Mahdi J, Goyal MS, Griffith J, Morris SM, Gutmann DH. Nonoptic pathway tumors in children with neurofibromatosis type 1. Neurology. 2020;95(8):e1052–e1059.