1-1-2022

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Nicole M Brossier

Jennifer M Strahle

Samuel J Cler

Michael Wallendorf

David H Gutmann

Neuro-Oncology Advances

4(1), 1–3, 2022 | https://doi.org/10.1093/noajnl/vdab187 | Advance Access date 27 December 2021

Brief Communication

Children with supratentorial midline pilocytic astrocytomas exhibit multiple progressions and acquisition of neurologic deficits over time

Nicole M. Brossier[†], Jennifer M. Strahle[†], Samuel J. Cler, Michael Wallendorf, and David H. Gutmann

Department of Pediatrics, Washington University School of Medicine, St. Louis, Missouri, USA (N.M.B.); Department of Neurosurgery, Washington University School of Medicine, St. Louis, Missouri, USA (J.M.S., S.J.C.); Department of Biostatistics, Washington University School of Medicine, St. Louis, Missouri, USA (M.W.); Department of Neurology, Washington University School of Medicine, St. Louis, Missouri, USA (D.H.G.)

Corresponding Author: David H. Gutmann, MD, PhD, Department of Neurology, Washington University, Box 8111, 660 South Euclid Avenue, St. Louis, MO 63110, USA (gutmannd@wustl.edu).

[†]*These authors contributed equally to this work.*

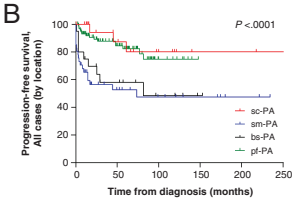
Pilocytic astrocytomas (PAs) are the most common brain tumors of childhood[1] and can arise anywhere within the neuroaxis, including the posterior fossa (pf-PA), supratentorial midline (sm-PA; including optic pathway, hypothalamus, thalamus), supratentorial cortex (sc-PA), brainstem (bs-PA), and spinal cord (sp-PA). While tumor location (sm, bs) has been proposed as a prognostic factor associated with poor progression-free survival (PFS),[2–4] 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).

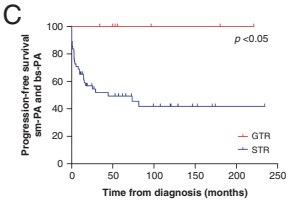
To remove resection status as a confounding variable, we subsequently analyzed the outcomes of children with STR PAs (n = 81) by brain location. While the overall percentage of cases that demonstrated radiographic evidence of progression was not different between groups, we found that more children with sm-PA had two or more progression events (Figure 1D), and 75% of subjects with three or more progression events harbored sm-PAs (not shown). Furthermore, the only children in our cohort with leptomeningeal dissemination or death harbored sm-PAs (Figure 1D). Consistent with these observations, no differences in PFS by location were observed between subjects with STR PAs at initial progression (Figure 1E); however, those with sm-PAs exhibited shorter times to second progression (Figure 1F).

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.

A Demographics by PA location.

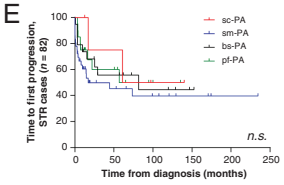
	Posterior Fossa, pf-PA (n = 101)	Supratentorial midline, sm-PA (n = 41)	Brainstem, bs-PA (n = 22)	Supratentorial cortical, sc-PA (n = 22)	Spinal, sc-PA (n = 22)	Overall, (n = 191)	p-value
Median age at diagnosis, yrs [range]	9.05 [1.06 – 18.22]	10.12 [1.01 – 17.89]	11.04 [1.88 – 17.67]	12.15 [2.75 – 17.89]	10.91 [3.18 – 14.54]	10.35 [1.01 – 18.22]	<0.05
Sex (Male, %)	50 (49.5%)	23 (56.1%)	11 (50%)	10 (45.5%)	3 (60%)	97 (50.8%)	*n.s.*
Resection (GTR, %)	81 (80%)	5 (12%)	3 (14%)	18 (82%)	3 (60%)	110 (58%)	<0.0001

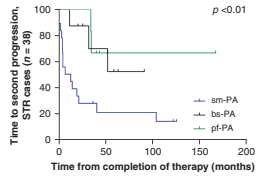


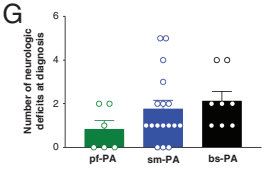


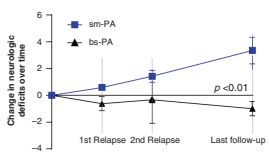
D Outcomes of STR PAs by location.

	pf-PA (n = 21)	sm-PA (n = 36)	bs-PA (n = 19)	p-value
Progression				
No progression	12 (57%)	17 (47%)	10 (53%)	
One progression	7 (33%)	4 (11%)	6 (32%)	<0.05
Two or more progressions	2 (10%)	15 (42%)	3 (16%)	
Other outcomes measures				
Leptomeningeal dissemination	0	3 (8%)	0	*n.s.*
Death	0	2 (6%)	0	*n.s.*









I Mutations in PA by location.

Molecular testing available	pf-PA (n = 31)	sm-PA (n = 16)	bs-PA (n = 9)	p-value
BRAF fusion identified	30 (97%)	10 (63%)	7 (78%)	<0.001
Other mutations identified	5 (16%)	8 (50%)	3 (33%)	<0.05
No mutations identified	0 (0%)	4 (25%)	1 (11%)	
Single mutation identified	28 (90%)	8 (50%)	6 (67%)	<0.005
Multiple mutations identified	3 (10%)	4 (25%)	2 (22%)	

Figure 1. Children with supratentorial midline pilocytic astrocytomas (PAs) exhibit greater rates of progression and acquisition of neurologic deficits over time. (A) One hundred ninety-one evaluable subjects with biopsy-proven PA were treated at St. Louis Children's Hospital between 2003 and 2021. While no differences in male/female incidence by brain location were observed, differences in the age at initial presentation were noted between subjects with pf-PA vs sc-PA (1-way ANOVA with correction for multiple comparisons using a Tukey post hoc test, $P < 0.05$). Gross total resection (GTR) was also different by location, with sm-PA and bs-PA having a higher percentage of subtotal resection (STR) tumors ($P < 0.0001$; Fisher's exact test). (B) Progression-free survival (PFS) differed by PA location, with subjects harboring sm-PA and bs-PA tumors demonstrating shorter PFS (Mantel-Cox log-rank test; $P < 0.0001$). (C) Longer PFS was observed in sm-PA and bs-PA subjects with a GTR relative to those with a STR ($P < 0.0001$; Mantel-Cox log-rank test). (D) Subjects with sm-PAs displayed higher rates of multiple progression events ($P < 0.05$; Fisher's exact test). All cases of leptomeningeal dissemination and death occurred in subjects with sm-PA. (E) There was no difference in PFS from diagnosis to first relapse by location. (F) Subjects with sm-PA exhibited shorter PFS from the completion of initial therapy to the second relapse ($P < 0.01$; Mantel-Cox log-rank test). (G) There were no significant differences in the number of neurologic deficits by brain location at diagnosis. (H) The change in number and severity of neurologic deficits was quantitated in subjects with sm-PA and bs-PA at first relapse, second relapse, and last follow-up date compared to initial diagnosis. Subjects with sm-PA had a greater accumulation of neurologic deficits over time than those with bs-PA ($P < 0.01$, mixed-effects analysis). (I) In subjects for whom tumor molecular testing data were available, those with sm-PA showed a significantly lower percentage of *BRAF* fusions ($P < 0.001$) and a higher percentage of both non-*BRAF* mutations ($P < 0.05$) and multiple mutations ($P < 0.005$) relative to pf-PA.

Given that different driver mutations may also affect clinical prognosis in pediatric low-grade glioma (pLGG),[5] 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), *BRAF*^{V600E} 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),[5,6] 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,[2,4] 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.[7] This discrepancy may be due to methodology, as our study included only subjects with PA,

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excluded those with GTR, and removed individuals with NF1, who often develop sm-LGG with a more indolent course.[8,9] 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.[10]

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.

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