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Anesthesia Exposure during Therapy Predicts Neurocognitive Outcomes in Survivors of Childhood Medulloblastoma

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Abstract

Objective: To examine the contribution of anesthesia exposure during treatment for childhood medulloblastoma to neurocognitive outcomes 3 years after tumor diagnosis.

Study design: In this retrospective study, anesthesia data were abstracted from medical records for 111 patients treated with risk-adapted protocol therapy at St. Jude Children's Research Hospital. Neurocognitive testing data were obtained for 90.9% of patients.

Results: For the 101 patients (62.4% male) who completed testing, mean age at diagnosis was 10.1 years and 74.3% were staged to have average-risk disease. Anesthesia exposure during treatment ranged from 1–52 events (mean = 19.9); mean cumulative duration per patient was 21.1 hours (range 0.7–59.7). Compared with normative expectations (16%), the group had a significantly higher frequency of at-risk scores (<1 SD) on measures of intelligence (28.7%), attention (35.2%), working memory (26.6%), processing speed (46.7%), and reading (25.8%). Including anesthesia exposure duration to linear regression models accounting for age at diagnosis, treatment intensity, and baseline IQ significantly increased the predicted variance for intelligence (r^2=.59), attention (r^2 =.29), working memory (r^2=.31), processing speed (r^2=.44), and reading (r^2=.25; all *P* values <.001).

Conclusion: In survivors of childhood medulloblastoma, a neurodevelopmentally vulnerable population, greater exposure to anesthesia significantly and independently predicts deficits in neurocognitive and academic functioning. When feasible, anesthesia exposure during treatment should be reduced.

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Medulloblastoma is the most common malignant childhood brain tumor. Five-year survival rates are 70–85% with contemporary multi-modal therapy that includes surgery, risk-adapted craniospinal irradiation, and adjuvant chemotherapy. (1) Survivors are at risk for treatment-related cognitive and academic declines. (2–4) Disease and treatment-related risk factors, including higher intensity of central nervous system-directed therapy, younger age at diagnosis, and treatment-related sequelae (5–9), do not fully account for variance in outcomes.

The US Food and Drug Administration has issued a warning about repeated anesthesia exposure in young children (10), citing animal and human studies that suggest a potential deleterious impact on neurodevelopment, learning, and cognition. (11–18) Findings from preclinical studies show a relationship between anesthesia dosage and the extent of neuronal apoptosis (19, 20) and subsequent deficits in learning and memory (21–23), particularly for animals treated during critically sensitive neurodevelopmental periods. Data from retrospective studies in humans suggest that anesthesia exposure during neurodevelopmentally vulnerable periods of development may be associated with decreased academic outcomes (16), particularly with longer duration or multiple exposures (12, 13, 15, 17). Two prospective studies found no association between single anesthesia exposure of a short duration and subsequent academic achievement (24) or frequency of autism spectrum diagnosis. (25)

These findings suggest the potential for adverse consequences of anesthesia exposure in early childhood. However, limitations including birth cohort design, lack of clinical details about participants, poorly specified outcomes, and lack of variability in anesthesia exposure (ie, single exposure, relatively short duration) make interpretation challenging. Many studies also have focused on drugs that are no longer in frequent use, and thus findings are limited by treatment era effects.

Children treated for medulloblastoma receive anesthesia for procedures during therapy, including surgery, radiation therapy, and neuroimaging. The association between anesthesia exposure and neurocognitive outcomes in survivors of childhood medulloblastoma has not been previously investigated. Understanding the contribution of anesthesia to neurocognitive outcomes in this vulnerable population is critical, given their young age as well as disease and treatment-related impacts on central nervous system development. We examined the effect of anesthesia exposure during protocol therapy to neurocognitive outcomes in early survivorship.

Methods

A total of 327 patients 3–21 years old with histologically confirmed medulloblastoma were consecutively enrolled in an IRB-approved, multisite clinical trial for patients with newly diagnosed embryonal brain tumor between 9/2003 and 3/2013 (SJMB03; ClinicalTrials.gov: NCT00085202). The current study includes only the subgroup of patients enrolled and treated at St. Jude Children’s Research Hospital (n =155). We excluded 2 patients due to a medical course that included prolonged sedation in the context of intubation and mechanical ventilation. Anesthesia exposure data were abstracted for a total of 153 patients. Of these, 42

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were not eligible for protocol-directed neurocognitive testing at 3 years post diagnosis (ie, did not consent, n=3; inadequate English proficiency or psychological or sensorimotor condition that precluded participation, n=12; off study or off treatment due to death or progressive disease, n=27). Of the 111 eligible patients, neurocognitive data were obtained for 101 patients (90.1%). Data were missing due to missed appointments due to medical status or patient refusal (n =10).

Patients underwent surgical resection and were classified as having average-risk medulloblastoma (≤1.5 cm^2 residual tumor and no metastatic disease) or high-risk medulloblastoma (>1.5 cm^2 residual disease and/or metastatic disease localized to the neuraxis), according to a modified Chang staging system. (26) Following enrollment on SJMB03, risk-adapted radiation therapy was initiated within 31 days of surgery. Radiation therapy for patients with high-risk disease included craniospinal irradiation (CSI; [M0–1, 36 Gy; M2–3, 36–39.6 Gy]) and supplemental photon irradiation to the tumor bed using conformal treatment methods (total dosage, 55.8 Gy). When appropriate, local sites of metastasis received supplemental photon irradiation (total dosage, 50.4–54 Gy). Patients with average-risk disease were treated with lower CSI (23.4 Gy) and supplemental conformal photon irradiation to the tumor bed (total dose, 55.8 Gy). The clinical target volume to the tumor bed was 1.0 cm for all patients. Following radiation therapy, at approximately 12 weeks post-treatment initiation, patients were treated with four cycles of high-dose chemotherapy (cyclophosphamide, cisplatin, and vincristine) with peripheral blood stem cell support.

Neurocognitive assessments were scheduled at baseline (after surgical resection and within 2 weeks of initiating radiation therapy), upon completion of radiation therapy, and annually for 5 years post-diagnosis. This study reports on outcomes obtained at 3 years post-diagnosis. Assessments were administered by psychological examiners or clinical research assistants under supervision of a licensed psychologist.

Neurocognitive outcomes included global intelligence (General Intellectual Ability), Broad Attention, Working Memory, and Processing Speed cluster scores from the Woodcock Johnson Tests of Cognitive Abilities, Third Edition, and the Broad Reading cluster score from the Woodcock Johnson Tests of Academic Achievement, Third Edition.(27, 28) All measures are normed on nationally representative data. Scores are age standardized with a population mean of 100 and standard deviation (SD) of 15. Lower scores indicate poorer performance. Standardized scores (SS) below the 16th percentile (SS ≤ 84) are considered at-risk. The selection of these outcomes from the broader neurocognitive assessment battery was empirically and theoretically driven. Specifically, we restricted the current analyses to include only those neurocognitive outcomes with group means and at-risk frequencies that significantly differed from normative expectations at $p \leq .01$ (Table I; available at www.jpeds.com). These neurocognitive domains have been shown to particularly vulnerable to in studies of survivors of childhood medulloblastoma (5, 6, 8, 29).

Medical record abstraction was performed to capture data for all anesthesia exposure events occurring between the date of study enrollment and one-year follow-up. Variables included the indication (procedure), agents, and cumulative dosages and total anesthesia duration.

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Records and coding were reviewed by a board-certified pediatric anesthesiologist and occurred between October 2015 and May 2016.

Statistical Analysis

Descriptive statistics were performed to characterize the overall group on relevant demographic and clinical variables. Frequency or mean comparisons (ie, Fisher exact test or independent samples t-test) were used to compare groups with and without neurocognitive data on relevant demographic and clinical variables to establish representativeness. Descriptive statistics were used to characterize anesthesia exposure and neurocognitive outcomes. Group mean neurocognitive scores were compared with normative data using a one-sample t-test. Chi-square was used to compare the frequency of at-risk scores in the group to the expected frequency in the normative population. Univariable methods were used to assess for the association between anesthesia exposure and established risk factors for neurocognitive effects. Bivariate correlation was used to examine the association between age at diagnosis and anesthesia exposure. One-way ANOVA was used to check if anesthesia exposure varied by treatment risk arm.

Linear regression was used to examine the factors predictive of neurocognitive outcomes. For the overall group (n=101), two models were tested for each neurocognitive outcome. First, we examined the association of known risk factors with neurocognitive outcomes (y =age at diagnosis + treatment risk arm). Anesthesia exposure was added to the second model (y=age at diagnosis + treatment risk arm + cumulative duration of anesthesia exposure). The variable of baseline intellectual functioning (ie, pre-treatment General Intellectual Ability score) was added to models that included the subset of patients who completed neurocognitive testing at study baseline (y=age at diagnosis + treatment risk arm + baseline IQ; y=age at diagnosis + treatment risk arm + baseline IQ + cumulative duration of anesthesia exposure). For both sets of models, we used ANOVA to compare the variance between the two models, to test the hypothesis that the full model adds explanatory value over the reduced model.

To explore the impact of surgery and complexity of medical course on our findings, we performed a secondary case-control analysis comparing neurocognitive outcomes between patients with posterior fossa syndrome (PFS) and a sample matched for sex, age at diagnosis, and treatment risk arm (1 case: 4 controls). Unless otherwise specified, all tests of statistical significance were two-sided. Data were analyzed using SAS® software, Version 9.4.

Results

Patient Demographic and Clinical Characteristics

Demographic and clinical characteristics for the overall group of patients eligible for neurocognitive testing (N=111) are presented in Table 2. The mean age at diagnosis was 10.0 years, 60.4% of patients were male, and 74.8% were treated for average-risk disease.

A total of 101 out of 111 eligible patients completed neurocognitive testing at 3 years post-diagnosis. On average, patients were 10.1 years old at diagnosis (SD=4.5) and 13.1 years old

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at assessment (SD=4.5). In those who completed testing, 62.4% were male and 74.3% were treated for average-risk disease. There were no significant differences between the groups with and without neurocognitive testing on the distribution of sex (male/female), treatment risk arm (average/high), or posterior fossa syndrome (yes/no). There were no significant differences between the group that completed testing and the group that did not complete testing on age at diagnosis or cumulative anesthesia exposure.

Of the 101 patients who completed neurocognitive testing at 3 years post diagnosis, 70 also had completed an assessment of global intellectual functioning prior to the initiation of radiation therapy (69.3%). Compared with the group who underwent baseline testing, patients without baseline testing data were significantly younger at diagnosis (mean[SD], 11.1[4.7] vs 7.9[3.1], $p = .001$) and had significantly greater cumulative anesthesia frequency (14.4[13.1] vs 31.9[15.7], $p \leq .001$) and duration (15.8[13.1] vs 33.1[15.2], $p \leq .001$. There was no significant difference between the groups with and without baseline testing with regard to sex ($P = .236$) or risk-arm distribution ($P = .992$).

Anesthesia Exposure for the Group Completing Neurocognitive Testing

The mean cumulative frequency of anesthesia exposure per patient was 19.9 events (SD 16.1, range 1–52) and the mean cumulative duration was 21.1 hours (*SD* 15.9, range 0.7–59.7). Anesthesia exposure indications included procedures (eg, lumbar puncture, bone marrow harvest, and placement of central lines), imaging (MRI or CT), and radiation therapy. Radiation therapy was the most common indication for anesthesia (52.9% of all recorded events; 42.6% of patients completing at least one fraction with anesthesia), followed by imaging (23.9% of all recorded events, 86.1% of patients completing at least one scan with anesthesia). Anesthesia was administered via inhalation, intravenous, or mixed (inhalation and intravenous) routes, depending on procedure.

The frequency of patients receiving each anesthetic agent and the cumulative dose of each agent are shown in Table 3. The most commonly used inhaled anesthetic was sevoflurane, with 91.9% of patients receiving it at least once. For intravenous administration, the most common agents were propofol and fentanyl, with 100% of patients receiving these agents at least once. Over all procedures, 2 to 6 unique agents were used. For inhaled agents, the average number per patient was 1.56. For intravenous agents, the average number per patient was 3.36.

Results from bivariate correlation analysis showed that anesthesia exposure varied significantly by age at diagnosis, with younger age predicting longer exposure duration ($r = -0.65$, $p < .0001$). Results from one-way ANOVA showed that anesthesia exposure varied significantly by treatment risk arm. Cumulative frequency was greater for patients treated for high-risk disease (mean =24.8 events, SD = 17.6) compared with the group treated for average-risk disease (mean events =18.1, SD = 15.3, $p=.07$), but this difference did not reach statistical significance. Cumulative duration was significantly greater for the high-risk group (mean = 27.7 hours, SD=18.8) compared with the average-risk group (mean = 18.9 hours, SD = 14.1, $p = .014$).

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Neurocognitive Outcomes at Three Years Post Diagnosis

Descriptive statistics for neurocognitive outcomes are shown in Table 4. Group mean scores were within the average to low-average range for all measures. Results from one-sample t-tests showed that group means were significantly different from normative expectations at $p < 0.01$. Group means were significantly lower on measures of global intelligence (94.9, SD = 17.9, $p = .008$), attention (89.1, SD = 17.9, $p < .0001$), working memory (93.6, SD = 16.9, $p = .0004$), processing speed (82.2, SD = 22.2, $p < 0.0001$), and reading (93.7, SD = 14.8, $p = .0001$). Compared with normative expectations (16%), the group had a significantly greater frequency of at-risk scores on measures of global intelligence (at-risk =28.7%, $p = .0005$), attention (at-risk =35.2%, $p < .0001$), working memory (at-risk =26.6% $p = .0027$), processing speed (at-risk =46.7%, $p < .0001$), and reading (at-risk =25.8%, $p = .0064$).

Anesthesia exposure during therapy predicts neurocognitive outcomes three years post diagnosis

Compared with the model using predictors of age at diagnosis and treatment risk arm, the model using age at diagnosis, treatment risk arm, and cumulative duration of anesthesia exposure predicted a significantly greater amount of variance in global intelligence ($r^2 = 0.05, 0.20$; $p < .0001$), attention ($r^2 = 0.04, 0.14$, $p = .0016$), working memory ($r^2 = 0.02, 0.17$, $p < .0001$), processing speed ($r^2 = 0.09, 0.19$, $p = .0009$), and reading ability ($r^2 = 0.01, 0.10$, $p = .0023$; Table 5 [available at www.jpeds.com]). Compared with the model incorporating predictors of age at diagnosis, treatment risk arm, and baseline IQ, the model with age at diagnosis, treatment risk arm, baseline IQ, and cumulative duration of anesthesia exposure predicted a significantly greater amount of variance in global intelligence ($r^2 = 0.05, 0.20$; $p < .0001$), attention ($r^2 = 0.04, 0.14$, $p = .0016$), working memory ($r^2 = 0.02, 0.17$, $p < .0001$), processing speed ($r^2 = 0.09, 0.19$, $p = .0009$), and reading ability ($r^2 = 0.01, 0.10$, $p = .0023$; Table 6).

Models including cumulative duration of anesthesia exposure, baseline IQ, age at diagnosis, and treatment risk arm significantly predicted scores on measures of intelligence ($r^2 = 0.50, 0.59$, $p = .0002$), attention ($r^2 = 0.21, 0.29$, $p = .0109$), working memory ($r^2 = 0.20, 0.31$, $p = .0015$), processing speed ($r^2 = 0.41, 0.44$, $p = .0480$), and reading ($r^2 = 0.20, 0.25$. $p = .0362$).

Given preclinical data that suggests younger patients may be at greatest risk from anesthesia exposure, we examined the interaction between age at diagnosis and anesthesia exposure. After accounting for variability from age at diagnosis, risk arm, baseline IQ, and cumulative anesthesia duration, the interaction term was not statistically significant for any of the modeled outcomes (Table 7; available at www.jpeds.com).

Exploratory analyses

Demographic and clinical characteristics for subgroups of patients with and without posterior fossa syndrome are shown in Table 8 (available at www.jpeds.com). The groups did not significantly differ with regard to distribution of sex, distribution of risk arm, mean age at diagnosis, or mean age at assessment. Compared with the group who had posterior fossa syndrome (n = 20), patients without posterior fossa syndrome (n = 81) had a significantly higher cumulative duration of anesthesia ($p = < .0001$). Results from a case-

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control analysis comparing patients with and without posterior fossa syndrome are shown in Table 9 (available at www.jpeds.com). Analyses are adjusted for anesthesia exposure (cumulative duration, measured in hours). Compared with the group having posterior fossa syndrome, patients without posterior fossa syndrome had significantly higher scores on measures of intelligence (p =0.0359) and processing speed (p =0.0219). For the group without posterior fossa syndrome, after adjusting for age at diagnosis, risk arm, and baseline IQ, increased duration of anesthesia significantly and independently predicted variability on all neurocognitive and academic outcomes (Table 10; available at www.jpeds.com). These results suggest that the adverse impact of anesthesia exposure on neurocognitive outcomes is evident in patients without posterior fossa syndrome, and account for a similar magnitude of variance in outcomes.

Discussion

The current study examined the contribution of anesthesia exposure during protocol-directed treatment for pediatric medulloblastoma to neurocognitive outcomes obtained three years post diagnosis. Anesthesia data were well-characterized and reflective of current practice. Neurocognitive data were obtained prospectively, and the test battery includes measures with established reliability, validity, and clinical utility.

This study yielded novel data characterizing anesthesia exposure during protocol-directed treatment for pediatric medulloblastoma. Over a 12-month period, patients were exposed to general anesthesia an average of 19 times, for an average cumulative duration of over 21 hours. Younger patients received general anesthesia more frequently and for a longer cumulative duration. This finding is notable, as studies from the general childhood population suggest that younger children are at the highest risk for anesthesia-related problems with learning and cognition. Radiation therapy treatment accounted for the majority of cumulative anesthesia exposures across the entire group; however, nearly half of all patients completed all radiation therapy treatments without anesthesia, suggesting that radiation therapy may be a potential target for behavioral interventions focused on reducing the need for anesthesia exposure during treatment.

This study examines the contribution of anesthesia exposure during treatment in survivors of childhood brain tumor, a neurodevelopmentally vulnerable population at significant risk for disease and treatment-related neurocognitive deficits. Findings from a recently published retrospective study examining the association between anesthesia exposure during therapy for childhood acute leukemia and neurocognitive outcomes in survivorship are similar to the current study (30). Notably, patients in that prior study were significantly older at diagnosis (14 years old). Together, these findings from childhood cancer survivors suggest that the period of neurodevelopmental vulnerability may be significantly longer in pediatric medical populations (ie, the most likely to have higher exposure to anesthesia).

Our findings on neurocognitive outcomes three years post diagnosis are largely consistent with prior studies in survivors of pediatric medulloblastoma. (6–9) Three years after study enrollment, the overall group of survivors had an elevated frequency of at-risk scores on measures of neurocognitive and academic skills compared with normative expectations, with

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specific areas of vulnerability including attention, processing speed, and working memory. Younger age at diagnosis was a risk factor for lower scores and higher ratings of problem behavior in daily life across nearly all measured domains.

Our finding that neurocognitive outcomes three years after diagnosis did not significantly differ by treatment risk arm is somewhat unexpected, as higher intensity of CNS-directed therapy is a well-recognized risk factor for poorer neurocognitive outcomes. Prior studies of neurocognitive outcomes in survivors of medulloblastoma treated on SJMB03 have identified the intensity of treatment (ie, risk arm) as a significant contributor to the decline in neurocognitive and academic performance that is seen one to five years after diagnosis. (8, 9) It is possible that the impact of risk arm on these outcomes emerges over time, such that the differences by risk arm are more evident at later study time points.

Models including age at diagnosis, treatment risk arm, and anesthesia exposure significantly predicted variance in neurocognitive outcomes. In all instances the amount of variance accounted for by the three-factor model was notably greater than that predicted by a two-factor model. Findings were similar for models that included baseline IQ as an additional predictor. Results from exploratory analysis in a subgroup of patients without posterior fossa syndrome are consistent with the findings from primary models. These results strongly support our hypothesis about the contribution of anesthesia exposure to neurocognitive outcomes.

From a clinical perspective, we suggest that alternatives to anesthesia exposure be considered when feasible (ie, when alternative measures exist to provide analgesic effects or to limit motion and increase compliance). Programmatic efforts to reduce anesthesia use may improve patient experience, reduce associated costs, and increase efficiency. Evidence-based behavioral interventions for promoting nonsedated scans have been implemented successfully in pediatric populations. (31–38) A survey of 101 parents of patients treated for childhood cancer at our institution supports the perceived feasibility and acceptability of nonsedated MRI examinations. (39)

Our study is not without limitations. Anesthesia data prior to treatment were not available. Data on anesthesia exposure are restricted to the first twelve months after enrollment on a clinical treatment trial. All cancer-directed therapy, including radiation therapy, was completed during this period. Protocol-directed indications for anesthesia exposure substantially decrease during the follow-up period. Nevertheless, the total exposure is not known for patients in the sample, and may slightly exceed the reported duration.

We compared neurocognitive outcomes to nationally representative normative data; however, it would not have been feasible to recruit a control group with the same diagnosis that completed treatment (ie, radiation therapy, neuroimaging, and procedures) without exposure to anesthesia. In the context of limitations of a retrospective study, our findings contribute meaningful information about the additive risk anesthesia exposure during protocol-directed, risk-adapted treatment for pediatric medulloblastoma. Future studies should prospectively collect anesthesia exposure data to more precisely characterize risk.

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Table 1 - Online.

Descriptive statistics for neurocognitive outcomes

	N	Mean	SD	Mean difference	p[a]	% At Risk[b]	p[c]
Woodcock Johnson Tests of Cognitive Abilities, 3rd Edition (SS)							
General Intellectual Ability	94	94.9	17.9	5.0	**0.0080**	28.7	**0.0005**
Broad Attention	88	89.1	17.9	10.9	< **0.0001**	35.2	< **0.0001**
Working Memory	94	93.6	16.9	6.4	**0.0004**	26.6	**0.0027**
Processing Speed	92	82.2	22.2	17.8	< **0.0001**	46.7	< **0.0001**
Woodcock Johnson Tests of Achievement, 3rd Edition (SS)							
Broad Reading	89	93.7	14.8	6.3	< **0.0001**	25.8	**0.0064**
Broad Math	93	93.9	15.8	6.0	**0.0004**	21.5	0.1017
Continuous Performance Test, 2nd Edition (T)							
Omissions	79	53.3	17.9	3.3	0.1083	15.2	0.7850
Hit Reaction Time	79	53.4	12.9	3.4	0.0244	25.3	**0.0141**
Variability	79	52.6	9.5	2.6	0.0164	21.5	0.1017
Discriminability	79	53.5	9.6	3.5	0.0017	25.3	0.0141
Response Style	79	50.9	9.9	0.9	0.4339	13.9	0.5854
Child Behavior Checklist (T)							
Attention Problems	81	56.0	7.8	6.0	< **0.0001**	24.7	0.0141
Behavior Rating Inventory of Executive Function (T)							
Global Executive Composite	82	51.8	12.4	1.8	0.1949	26.8	**0.0027**

Abbreviations: SS = Standard Score, T = T-score; SD = standard deviation. Standard Score population mean = 100, SD = 15; T-score population mean = 50, SD = 10. Bold font = statistically significant at p ≤ 0.001.

a: two-tailed p-value from a one-sample t-test comparing the group mean to normative expectations.

b: frequency of scores 1 SD outside the normative mean.

c: two-sided p-value from frequency comparison (chi-Square) of the distribution of at-risk and not at-risk scores (percentage).

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Table 2.

Demographic and clinical characteristics

		Overall Group N = 111		Completed Testing n = 101		No Testing n = 10		
		n	***%***	***n***	***%***	***n***	***%***	***p*** [a]
Sex	Male	67	60.4	63	62.4	4	40.0	0.168
	Female	44	39.6	38	37.6	6	60.0	
Race	White	83	74.8	77	76.2	6	60.0	
	Black	15	13.5	13	12.9	2	20.0	
	Asian	5	4.5	4	4	1	10.0	
	Mixed Race, Other	8	7.2	7	6.9	1	10.0	
Risk Arm	Average	83	74.8	75	74.3	8	80.0	0.690
	High	28	25.2	26	25.7	2	20.0	
Posterior Fossa Syndrome	Yes	22	19.8	20	19.8	2	20.0	0.988
	No	89	80.2	81	80.2	8	80.0	
		Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Age at Diagnosis		10.0	4.5	10.1	4.5	9.0	4.6	0.452
Anesthesia Exposure	Cumulative Frequency	19.9	16.0	19.8	16.1	20.4	15.7	0.775
	Cumulative Duration	21.3	15.8	21.1	15.9	22.6	15.9	0.914

Abbreviations: SD = standard deviation. Age is reported in years and months. Anesthesia exposure duration reported in hours.

Notes:

[a] two-sided p-values from statistical comparisons between groups with and without neurocognitive testing (Chi-square or independent samples t-test).

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Table 3.

Frequency and cumulative dose for inhaled and intravenous anesthesia agents

		Patients receiving agent		Cumulative Exposure per Patient				
		n	**%**	***Mean***	***SD***	***Median***	***Min***	***Max***
Inhaled Agents	Sevoflurane	92	91.09	1.83	1.27	2.00	0.00	6.00
	Nitrus Oxide	47	46.53	0.62	0.85	0.00	0.00	4.00
	Isoflurane	15	14.85	0.18	0.48	0.00	0.00	3.00
	Desflurane	5	4.95	0.05	0.22	0.00	0.00	1.00
	Halothane	1	0.99	0.01	0.10	0.00	0.00	1.00
		Patients receiving agent		**Cumulative Dose per Patient**				
Intravenous Agents	Propofol (mg/kg)	101	100	6169.92	5345.35	4055.00	150.00	24846.00
	Fentanyl (mcg/kg)	101	100	327.11	297.28	200.00	50.00	1465.00
	Midazolam (mg/kg)	61	60.4	5.87	11.37	1.00	0.00	70.00
	Morphine (mg/kg)	27	26.73	2.95	11.64	0.00	0.00	85.00
	Pentobarbitol (mg/kg)	18	17.82	53.32	141.56	0.00	0.00	910.00
	Meperidine (mg/kg)	13	12.87	13.58	48.16	0.00	0.00	380.00
	Ketamine (mg/kg)	9	8.91	30.55	130.87	0.00	0.00	769.61
	Lorazepam (mg/kg)	5	4.95	0.07	0.38	0.00	0.00	3.00
	Hydromorphone (mg/kg)	2	1.98	0.02	0.20	0.00	0.00	2.00
	Clonidine (mg/kg)	1	0.99	0.00	0.01	0.00	0.00	0.10
	Dexmedetomidine (mg/kg)	0	0	0.00	0.00	0.00	0.00	0.00

N = 101. Abbreviations: SD = standard deviation; Min = minimum; Max = Maximum; mg = milligram; mcg = microgram; kg = kilogram

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Table 4.

Descriptive statistics for neurocognitive outcomes at three years post-diagnosis

	N	Mean	SD	Mean difference	p[a]	% At Risk[b]	p[c]
Woodcock Johnson Tests of Cognitive Abilities, 3rd edition (SS)							
General Intellectual Ability	94	94.9	17.9	5.0	**0.0080**	28.7	**0.0005**
Broad Attention	88	89.1	17.9	10.9	< **0.0001**	35.2	< **0.0001**
Working Memory	94	93.6	16.9	6.4	**0.0004**	26.6	**0.0027**
Processing Speed	92	82.2	22.2	17.8	< **0.0001**	46.7	< **0.0001**
Woodcock Johnson Tests of Achievement , 3rd edition (SS)							
Broad Reading	89	93.7	14.8	6.3	< **0.0001**	25.8	**0.0064**

Abbreviations: SS = Standard Score, population mean = 100, SD = 15; Bold font = statistically significant at $p \leq 0.001$.

a: two-tailed p-value from a one-sample t-test comparing the group mean to normative expectations

b: frequency of scores 1 SD outside the normative mean

c: two-sided p-value from frequency comparison (Chi-Square) of the distribution of at-risk and not at-risk scores (percentage).

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Table 5 – Online.

Linear regression of cumulative anesthesia duration predicting neurocognitive outcomes, models including age at diagnosis and treatment risk arm

Outcome	Model	Variables	*Parameter Estimate*	*SE*	*T*	*P (a)*	*R (2) Adjusted*	*R (2) Change*	*F-Value*	*p (b)*
	1	Age at Diagnosis	0.89	0.41	2.15	**0.0345**	0.05			
		Risk Arm	−4.93	4.14	−1.19	0.2377				
General Intellectual Ability	2	Age at Diagnosis	−0.45	0.49	−0.93	0.3566	0.20	0.15	18.96	**<.0001**
		Risk Arm	−0.83	3.90	−0.21	0.8314				
		Anesthesia Duration	−0.62	0.14	−4.35	< **0.0001**				
	1	Age at Diagnosis	0.84	0.43	1.98	**0.0507**	0.04			
		Risk Arm	−4.58	4.35	−1.05	0.2963				
Broad Attention	2	Age at Diagnosis	−0.34	0.54	−0.62	0.5341	0.14	0.10	10.61	**0.0016**
		Risk Arm	−1.27	4.03	−0.30	0.7653				
		Anesthesia Duration	−0.54	0.17	−3.26	**0.0016**				
	1	Age at Diagnosis	0.66	0.40	1.65	0.102	0.02			
		Risk Arm	−0.32	3.93	−0.82	0.417				
Working Memory	2	Age at Diagnosis	−0.61	0.47	−1.29	0.199	0.17	0.15	18.09	**<.0001**
		Risk Arm	0.21	3.69	0.06	0.9542				
		Anesthesia Duration	−0.59	0.14	−4.25	**<0.0001**				
	1	Age at Diagnosis	1.66	0.51	3.26	**0.0016**	0.09			
		Risk Arm	−0.06	5.21	−0.01	0.9908				
Processing Speed	2	Age at Diagnosis	0.31	0.62	0.50	0.6189	0.19	0.10	11.86	**0.0009**
		Risk Arm	3.77	5.04	0.75	0.4565				
		Anesthesia Duration	−0.63	0.18	−3.44	**0.0009**				
	1	Age at Diagnosis	0.32	0.36	0.89	0.3765	0.01			
		Risk Arm	−4.57	3.59	−1.27	0.2067				
Broad Reading	2	Age at Diagnosis	−0.35	0.40	−0.88	0.3829	0.10	0.09	9.87	**0.0023**
		Risk Arm	−2.48	3.48	−0.71	0.4773				
		Anesthesia Duration	−0.39	0.12	−3.14	**0.0023**				

Abbreviations: SE = Standard Error. Bold font = statistically significant at $p \leq 0.05$.

a: 2-sided p-value from comparison of parameter estimate to 0.

b: 2-sided p-value from ANOVA comparison of regression models. Anesthesia duration is measured in hours.

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Table 6.

Linear regression of cumulative anesthesia duration predicting neurocognitive outcomes, adjustung for age at diagnosis, treatment risk arm, and baseline global intellectual ability

Outcome	Model	Variables	*Parameter Estimate*	*SE*	*T*	*p (a)*	*R (2) Adjusted*	*R (2) Change*	*F-value*	*p (b)*
	1	Age at Diagnosis	1.08	0.32	3.34	**0.0014**	0.50			
		Risk Arm	−12.04	3.44	−3.51	**0.0009**				
		Baseline IQ	0.78	0.10	7.81	**<.0001**				
General Intellectual Ability	2	Age at Diagnosis	0.04	0.39	0.11	0.9135	0.59	0.09	15.51	**0.0002**
		Risk Arm	−7.04	3.34	−2.11	**0.0390**				
		Baseline IQ	0.71	0.09	7.77	**<.0001**				
		Anesthesia Duration	−0.55	0.14	−3.94	**0.0002**				
	1	Age at Diagnosis	0.92	0.41	2.23	**0.0293**	0.21			
		Risk Arm	−9.60	4.66	−2.06	**0.0440**				
		Baseline IQ	0.54	0.13	4.12	**0.0001**				
Broad Attention	2	Age at Diagnosis	−0.04	0.54	−0.08	0.9367	0.29	0.09	6.93	**0.0109**
		Risk Arm	−5.91	4.66	−1.27	0.2100				
		Baseline IQ	0.51	0.13	4.08	**0.0001**				
		Anesthesia Duration	−0.53	0.20	−2.63	**0.0109**				
	1	Age at Diagnosis	0.64	0.39	1.63	0.1082	0.20			
		Risk Arm	−8.47	4.15	−2.04	**0.0459**				
		Baseline IQ	0.51	0.12	4.24	**<.0001**				
Working Memory	2	Age at Diagnosis	−0.46	0.49	−0.94	0.3512	0.31	0.11	11.11	**0.0015**
		Risk Arm	−3.53	4.12	−0.86	0.3949				
		Baseline IQ	0.43	0.11	3.84	**0.0003**				
		Anesthesia Duration	−0.59	0.18	−3.33	**0.0015**				
	1	Age at Diagnosis	1.99	0.36	5.52	**<.0001**	0.41			
		Risk Arm	−7.87	4.03	−1.95	0.0554				
		Baseline IQ	0.58	0.11	5.12	**<.0001**				
Processing Speed	2	Age at Diagnosis	1.33	0.48	2.79	**0.0071**	0.44	0.03	4.08	**0.0480**
		Risk Arm	−5.19	4.15	−1.25	0.2153				
		Baseline IQ	0.55	0.11	4.98	**<.0001**				

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Outcome	Model	Variables	*Parameter Estimate*	*SE*	*T*	*p (a)*	*R (2) Adjusted*	*R (2) Change*	*F-value*	*p (b)*
		Anesthesia Duration	−0.36	0.18	−2.02	**0.0480**				
	1	Age at Diagnosis	0.48	0.31	1.54	0.1294	0.20			
		Risk Arm	−8.55	3.36	−2.55	**0.0133**				
		Baseline IQ	0.39	0.10	4.06	**0.0001**				
Broad Reading	2	Age at Diagnosis	−0.11	0.41	−0.27	0.7905	0.25	0.05	4.59	**0.0362**
		Risk Arm	−6.20	3.44	−1.80	0.0765				
		Baseline IQ	0.34	0.10	3.61	0.0006				
		Anesthesia Duration	−0.34	0.16	−2.14	**0.0362**				

Abbreviations: SE = Standard Error Bold font = statistically significant at $p \leq 0.05$.

a: 2-sided p-value from comparison of parameter estimate to 0.

b: 2-sided p-value from ANOVA comparison of regression models. Anesthesia duration is measured in hours.

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Table 7 – Online.

Linear regression model of cumulative anesthesia duration predicting neurocognitive outcomes, models including age at diagnosis, treatment risk arm, baseline global intellectual ability and interaction between age at diagnosis and cumulative anesthesia duration

Outcome	Variables	*Parameter Estimate*	*SE*	*T*	*p*	*R (2) Adjusted*
General Intellectual Ability	Age at Diagnosis	−0.08	0.49	−0.16	0.8761	0.62
	Risk Arm	−7.07	3.36	−2.10	**0.0396**	
	Baseline IQ	0.71	0.09	7.64	**<.0001**	
	Anesthesia Duration	−0.65	0.29	−2.29	**0.0256**	
	Anesthesia × Age at Diagnosis	0.02	0.04	0.42	0.6786	
Broad Attention	Age at Diagnosis	−0.09	0.67	−0.13	0.8966	0.33
	Risk Arm	−5.87	4.71	−1.25	0.2181	
	Baseline IQ	0.51	0.13	4.03	**0.0002**	
	Anesthesia Duration	−0.57	0.40	−1.43	0.1578	
	Anesthesia Duration × Age at Diagnosis	0.01	0.06	0.11	0.9096	
Working Memory	Age at Diagnosis	−0.64	0.61	−1.05	0.2996	0.36
	Risk Arm	−3.62	4.15	−0.87	0.3874	
	Baseline IQ	0.44	0.12	3.84	**0.0003**	
	Anesthesia Duration	−0.74	0.35	−2.08	**0.0418**	
	Anesthesia Duration × Age at Diagnosis	0.02	0.05	0.49	0.6241	
Processing Speed	Age at Diagnosis	1.62	0.59	2.75	**0.0080**	0.48
	Risk Arm	−5.42	4.17	−1.30	0.1980	
	Baseline IQ	0.54	0.11	4.85	**<.0001**	
	Anesthesia Duration	−0.10	0.35	−0.29	0.7731	
	Anesthesia Duration × Age at Diagnosis	−0.04	0.05	−0.84	0.4050	
Broad Reading	Age at Diagnosis	−0.30	0.52	−0.58	0.5648	0.30
	Risk Arm	−6.32	3.46	−1.82	0.0731	
	Baseline IQ	0.35	0.10	3.64	**0.0006**	
	Anesthesia Duration	−0.51	0.33	−1.56	0.1252	
	Anesthesia Duration × Age at Diagnosis	0.02	0.04	0.60	0.5506	

Abbreviations: SE = Standard Error. Bold font = statistically significant at $p \leq 0.05$. 2-sided p-value from comparison of parameter estimate to 0. Anesthesia duration is measured in hours

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Table 8 – Online.

Demographic and clinical characteristics for patients with and without posterior fossa syndrome

		PFS-yes n = 20		PFS-no n = 81		
		n	**%**	**n**	**%**	**P***
Sex	Male	13	65.0	50	61.7	0.787
	Female	7	35.0	31	38.3	
Risk Arm	Average	14	70.0	61	75.3	0.627
	High	6	30.0	20	24.7	
		Mean	**SD**	**Mean**	**SD**	**p****
Age at Diagnosis		8.6	11.6	10.5	4.7	0.082
Cumulative Anesthesia Duration		33.7	16.1	18.0	14.3	**<.0001**
Age at Testing		11.6	3.2	13.5	4.7	0.095

PFS = posterior fossa syndrome.

*2-sided p-value from chi-square frequency comparison;

**2-sided p-value from two-sample t-test. Bold font = statistically significant at $p \leq 0.05$. Anesthesia duration is measured in hours.

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Table 9 - Online.

Results of ANCOVA comparing groups with or without posterior fossa syndrome (case-control)

	PFS-yes		PFS-no			
	Mean	***SD***	***Mean***	***SD***	***F***	***p*** [a]
General Cognitive Ability	80.89	14.27	97.47	19.90	4.59	**0.0359**
Broad Attention	75.50	16.89	92.00	20.87	2.56	0.1147
Working Memory	85.17	14.90	96.57	19.50	1.18	0.2816
Processing Speed	60.00	24.59	82.04	23.07	5.51	**0.0219**
Broad Reading	86.29	13.89	95.40	18.41	1.20	0.2781

Abbreviations: PFS = posterior fossa syndrome; SD = standard deviation

a: 2-tailed p-value from ANCOVA models controlling for duration of anesthesia exposure

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Table 10 – Online.

Linear regression of cumulative anesthesia duration predicting neurocognitive outcomes for patients without posterior fossa syndrome, adjusting for age at diagnosis, treatment risk arm, and baseline global intellectual ability

Outcome	Model	Variables	Parameter Estimate	SE	T	P (a)	R (2) Adjusted	R (2)Change
General Intellectual Ability	1	Age at Diagnosis	0.99	0.34	2.95	**0.0046**	0.49	
		Risk Arm	−12.90	3.56	−3.62	**0.0006**		
		Baseline IQ	0.76	0.10	7.51	**<.0001**		
	2	Age at Diagnosis	−0.09	0.41	−0.23	0.8201	0.59	0.10
		Risk Arm	−7.12	3.51	−2.03	**0.0472**		
		Baseline IQ	0.68	0.09	7.36	**<.0001**		
		Anesthesia Duration	−0.57	0.15	−3.92	**0.0002**		
Broad Attention	1	Age at Diagnosis	0.80	0.43	1.86	0.0687	0.19	
		Risk Arm	−10.34	4.86	−2.13	**0.0378**		
		Baseline IQ	0.51	0.13	3.83	**0.0003**		
	2	Age at Diagnosis	−0.24	0.56	−0.43	0.6687	0.28	0.09
		Risk Arm	−5.75	4.89	−1.17	0.2452		
		Baseline IQ	0.47	0.13	3.72	**0.0005**		
		Anesthesia Duration	−0.57	0.21	−2.72	**0.0089**		
Working Memory	1	Age at Diagnosis	0.52	0.41	1.27	0.2085	0.19	
		Risk Arm	−9.74	4.27	−2.28	**0.0264**		
	2	Baseline IQ Age at Diagnosis	0.49	0.12	4.02	**0.0002**	0.32	0.12
			−0.64	0.51	−1.25	0.2159		
		Risk Arm	−4.04	4.29	−0.94	0.3498		
		Baseline IQ	0.40	0.11	3.53	**0.0008**		
		Anesthesia Duration	−0.60	0.18	−3.34	**0.0015**		
Processing Speed	1	Age at Diagnosis	1.91	0.38	5.05	**<.0001**	0.38	
		Risk Arm	−7.11	4.25	−1.67	0.0999		
		Baseline IQ	0.57	0.12	4.83	**<.0001**		
	2	Age at Diagnosis Risk Arm	1.22	0.50	2.42	**0.0187**	0.41	0.03
			−3.85	4.44	−0.87	0.3894		
		Baseline IQ	0.53	0.12	4.64	**<.0001**		
		Anesthesia Duration	−0.38	0.19	−2.02	**0.0482**		
Broad Reading	1	Age at Diagnosis	0.53	0.33	1.59	0.1181	0.19	
		Risk Arm	−7.42	3.51	−2.11	**0.0392**		
		Baseline IQ	0.39	0.10	3.96	**0.0002**		
	2	Age at Diagnosis Risk Arm	−0.22	0.43	−0.51	0.6115	0.27	0.08
			−4.07	3.59	−1.13	0.2618		
		Baseline IQ	0.33	0.10	3.39	**0.0013**		
		Anesthesia Duration	−0.42	0.16	−2.58	**0.0125**		

N = 81. Abbreviations: SE = Standard Error Bold font = statistically significant at $p \leq 0.05$.

[a]: 2-sided p-value from comparison of parameter estimate to 0. Anesthesia duration is measured in hours.

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