RESEARCH ARTICLE

Congenital tumors of the central nervous system: an institutional review of 64 cases with emphasis on tumors with unique histologic and molecular characteristics

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Abstract

Congenital brain tumors are rare accounting for 0.5%–1.9% of all pediatric brain tumors. While different criteria have been used to classify a tumor as congenital, those diagnosed prior to 6 months of age are considered to be "probably" congenital in origin. We performed an institutional review of all central nervous system (CNS) tumors (surgical and autopsy specimens from 1990 to 2019) in patients less than 6 months old. Sixty-four unique cases were identified, and these accounted for 2.0% of all CNS tumor specimens at our institution. The most common tumor types were high-grade gliomas, low-grade gliomas and medulloblastomas. Atypical teratoid rhabdoid tumors, choroid plexus tumors and germ cell tumors also accounted for a significant portion of the cohort. Seven tumors were diagnosed prenatally. The most common clinical presentation at diagnosis was increased head circumference. At the conclusion of the study, over half of the patients were alive including all patients with WHO grade I and II tumors. Ninety-two percent of cases were classifiable using the 2016 WHO system, and when available, molecular findings supported the histologic diagnoses. However, several gliomas had unusual histologic features and did not correspond to a well-defined entity. Molecular testing was essential for accurate classification of a subset of these tumors, and several high-grade gliomas exhibited fusions considered unique to infantile gliomas, including those involving the *MET, ALK* and NTRK genes. To our knowledge, this cohort represents the largest single-institution study of congenital CNS tumors and highlights many ways in which congenital CNS tumors are distinct from CNS tumors of older pediatric patients and adults.

INTRODUCTION

By strictest definition, congenital central nervous system (CNS) tumors are present at or before birth. However, as some tumors may not be symptomatic at the time of birth, those presenting within the first few months of life are also likely congenital in origin. In the literature, the criteria used to classify a CNS tumor as being congenital varies greatly with cutoffs ranging between 4 weeks of life and 1 year at the time of symptom onset (2, 6, 8, 17–20, 29, 32, 34, 36). A few different classification schemes have been described. One of the earliest proposed was by Solitare and Krigman who subdivided brain tumors into the following groups: definitely congenital (already symptomatic at birth), probably congenital (symptomatic during the first week of life) and possibly congenital (symptomatic within the first 2–3 months) (35). A more recent classification system restricted the definition of possibly congenital tumors to tumors producing symptoms within the first 2 months of life (39). A subsequent classification by Ellams *et al* considered tumors diagnosed within the first 6 weeks of life to be congenital in origin, tumors presenting between 6 weeks and 6 months to be probably congenital and those presenting between 6 and 12 months of life to be possibly congenital (6).

As the definition of what constitutes a congenital CNS tumor has varied across studies, the incidence of these tumors also varies within the literature ranging between 1.1 and 3.4 per million live births (16). In patients less than 15 years of age, congenital brain tumors are thought to represent

0.5%–1.9% of all brain neoplasms; though some studies report rates as high as 4% (14, 23). The incidence of congenital CNS tumors has increased over time due to improved prenatal care and routine ultrasound scanning which allows for increased intrauterine detection (13, 17).

Historically the prognosis associated with these congenital CNS tumors has been poor with an overall survival of only 28% (12). However, outcomes have been reported to be improved in recent years with advancements in therapies (17, 20, 22, 24, 31, 33, 43). Outcome is also related to multiple factors including size, location and WHO grade. Not unexpectedly, higher-grade tumors are associated with higher mortality rates than low-grade neoplasms (17).

A variety of tumor types have been reported to present in the perinatal period including, but not limited to: teratomas, low- and high-grade gliomas, embryonal tumors, meningiomas and craniopharyngiomas. Teratomas are often regarded to be the most common type; however, these are less frequently encountered in older children (2, 12, 26, 28, 32, 36, 40). Congenital CNS tumors also differ from CNS tumors in older children in other ways including their predilection for the supratentorial compartment (2, 3, 9, 32) and initial clinical presentation (12, 20, 41).

Over the past decade, there has been a significant increase in molecular testing performed on brain tumor specimens which has led to the discovery that infantile CNS tumors, particularly the high-grade gliomas, have molecular characteristics that differ from tumors of older children. Specifically, alterations in *ALK, ROS1, MET,* NTRK and other genes are unique to high-grade gliomas of infants (4, 8, 9, 18).

In this study, we performed an institutional retrospective review of all CNS tumors in infants less than 6 months of age. To our knowledge, this is the largest single-institutional study of congenital CNS tumors. In addition to characterizing the clinical and histologic features of these rare neoplasms, we also focus on gliomas with molecular characteristics unique to CNS tumors of neonates and infants.

METHODS

This study was approved by an independent institutional review board at the Children's Hospital of Philadelphia. A database search was performed for surgical, consult and autopsy pathology cases from January 1, 1990 through December 31, 2019 to identify all CNS tumor specimens in infants under 6 months of age. Tumor location was restricted to those within the cranium and spinal canal; tumors of the sacrococcygeal region were excluded. For each patient identified in the database query, the electronic medical record was subsequently searched to obtain information regarding age at diagnosis, presenting symptoms, imaging findings, molecular testing and follow-up data. The data that support the findings of this study are available from the corresponding author upon reasonable request.

As several of the tumors identified in the database search had not been classified using the current, 2016 WHO Classification of Tumors of the Central Nervous System scheme (21), these cases were reviewed by a board certified neuropathologist (MS and/or AV) and reclassified using current criteria when possible. For the purposes of grouping tumors, medulloblastomas and atypical teratoid rhabdoid tumors (ATRTs) were considered separately from other embryonal tumors on the basis that both medulloblastomas and ATRTs are unique tumor entities with molecular profiles distinct from each other and other embryonal tumors.

Immunohistochemistry

When necessary, additional immunohistochemical stains were performed to facilitate the reclassification of tumors using the 2016 WHO classification system including molecular subgrouping of medulloblastomas. These immunohistochemical stains included: INI-1 (BD Biosciences, 612111, 1:100), BRG1 (Santa Cruz Biotechnology, sc-17796, 1:400), GFAP (Dako, 6F2, 1:400), synaptophysin (Dako, SY38, 1:100), neurofilament (Thermo Scientific, QL215385, 1:400), EMA (Dako, E29, 1:200), IDH1-R132H (Dianova, DIA-H09-L), ATRX (Sigma, HPA001906, 1:100), H3K27M (Sigma, SAB5600095, 1:1000), GAB1 (Santa Cruz Biotechnology, sc-133191, 1:400), YAP1 (Santa Cruz Biotechnology, sc-101199, 1:200), LEF1 (abcam, EPR2029Y, 1:100), beta-catenin (BD Biosciences, 610154, 1:1000) and p53 (Dako, DO-7, 1:100). Staining was performed on the Leica Bond-IIITM Autostainer using the Bond Polymer Refine Detection System (Leica Microsystems DS9800) with the DAB chromagen. Nuclei were counterstained with hematoxylin. Other immunostains that were previously performed as part of the initial clinical immunohistochemical workup included: vimentin, OLIG2, CD45, TdT, desmin, myoD1, myogenin, OCT4, HMB45, SOX10, AE1-3, transthyretin, CD31 and CD34.

Molecular analysis

Molecular testing was performed on a subset of the tumors (16/64) as part of the clinical workup. Single nucleotide polymorphism (SNP) microarray analysis was performed on four tumors and next generation sequencing (NGS) was performed on 12 tumors.

Single nucleotide polymorphism microarray analysis

Genome-wide SNP microarray analysis was performed on genomic DNA extracted from the tumor samples using the Illumina Infinium CytoSNP-850K BeadChip (Illumina, San Diego, CA) according to our standard protocol (5). The chip contains approximately 850 000 empirically selected single nucleotide polymorphisms (SNPs) spanning the entire genome with enriched coverage for 3262 genes of known cytogenetics relevance in both constitutional and cancer applications as defined by the International Collaboration for Clinical Genomics (ICCG) and the Cancer Genomics Consortium (CGC). The data were analyzed using CNV Workshop (7) and vendor provided analysis software (GenomeStudio). Deletions of ≥ 200Kb, duplications of ≥ 1Mb in a genomic region, loss of heterozygosity (LOH) of ≥ 5Mb or any changes below criteria but deemed to be clinically significant was reported.

Next generation sequencing

Our institution's NGS Comprehensive solid tumor panel includes sequence and copy number analyses of 238 cancer genes and evaluations of fusion genes associated with 110 cancer genes as previously described (38) (the genes included in the panel can be found at https://www.testmenu.com/chop/Tests/785967). For fusion analysis, target-specific primers covering 673 exons were custom designed to identify known fusion genes and potential novel fusion genes associated with 110 cancer genes using Anchored Multiplex PCR (AMP™) technology (ArcherDX, Inc. Boulder, CO). Total RNA (or total nucleic acid from FFPE samples) was extracted from the tumor samples and reverse-transcribed into cDNA. Libraries were constructed using ArcherTM Universal RNA Reagent Kit v2 for Illumina. Barcoded libraries were pooled and sequenced on Illumina HiSeq platform using 150 bp paired-end sequencing (Illumina, San Diego, CA). Sequence data were analyzed and visualized with Archer Analysis software using the JBrowse genome browser (Evolutionary Software Foundation, Berkeley, CA). For sequence variants (SNVs, single nucleotide variants, and indels, small insertion/deletions) and copy number variations (CNVs) analysis, genomic DNA was extracted from the tumor samples. Libraries were prepared using probes targeting 238 cancer genes, and sequenced on HiSeq platform using 150 bp paired-end sequencing. Sequence data were analyzed using the home brew software ConcordS v2 (for SNVs and indels) and NextGENe v2 NGS Analysis Software (for CNVs; SoftGenetics, LLC, State College, PA).

RESULTS

Sixty-five surgical and autopsy CNS tumor specimens from infants under 6 months of age were identified over a 30-year period via database search (Table 1). Sixteen of these tumors were included in a previously published study on the surgical treatment of congenital CNS tumors (19). These 65 specimens represented 2.0% of all CNS tumor specimens collected during this period. Of these specimens, 54 were surgical (including 10 consult cases) and 11 were autopsy derived; 64 were unique tumors (one patient underwent both surgical resection and autopsy, specimens #5 and 6, respectively). For all other autopsy cases, a prior surgical biopsy/resection was not performed. The 10 consult cases represented 1.8% of all CNS tumor consultations received during that same 30 year period. The most common types were high-grade gliomas (including glioblastoma and anaplastic astrocytoma) which accounted for 16% of all tumors; the remaining specimens included low-grade gliomas (primarily pilocytic astrocytomas, 12%), medulloblastomas (14%), choroid plexus tumors (13%), ATRTs (12%) and germ cell tumors (11%). Other tumor types included WHO-defined glioneuronal tumors (6%), other embryonal tumors which are neither medulloblastomas nor ATRTs (5%), and ependymomas (5%). Two cases of brain involvement by acute myeloid leukemia were also present, as well as one malignant tumor which showed both neuronal and glial features by immunostaining and one juvenile xanthogranuloma of the pons.

Forty-three tumors were from female patients and 21 from males (M:F = 1:2). All high- and low-grade gliomas and the majority of medulloblastomas were in females. Supratentorial location was seen in 64% of cases, including all choroid plexus tumors and glioneuronal tumors. The majority of high- and low-grade gliomas were also located supratentorially. In contrast, the majority of ATRTs were located in the posterior fossa.

Medulloblastomas were largely the desmoplastic/nodular histologic variant, and two tumors demonstrated classic histology. Immunostains to determine the molecular subgroup were performed on six tumors; five medulloblastomas with desmoplastic/nodular histology were assigned to the SHH-activated, *TP53*-wildtype molecular subgroup. One tumor with classic histology was classified as non-WNT/non-SHH subtype (Table 1). None of the medulloblastomas were genetically defined by methylation profile.

Information regarding patient age at time of symptom onset/presentation was available for 50 patients. Seven tumors (14%) were diagnosed on prenatal ultrasound and an additional 24 (48%) were identified in patients younger than 2 months of age (Figure 1A). The remaining 38% of the tumors presented between 2 and 6 months of age. The average age at the time of surgery/autopsy was 3.0 ± 1.8 months (mean ± standard deviation) with 77% of the specimens obtained when patients were between 2 and 6 months of age (Figure 1A). The patients with germ cell tumors and glioneuronal tumors all presented prenatally or shortly after birth (Figure 1B). Similarly, the majority of patients with medulloblastomas and high-grade gliomas also presented prenatally or within the first 2 months of life (Figure 1B).

The medical records of nine patients included information regarding prenatal ultrasounds, all performed at outside institutions. All seven patients whose tumors were diagnosed prenatally are included in this group (Table 1 and Figure 1). Two patients' tumors were identified on ultrasounds performed in the second trimester (tumors #1 and # 35). One patient with an immature teratoma (tumor #55) reportedly had a normal ultrasound at 18 weeks gestational age and was later diagnosed with an intracranial tumor on third trimester ultrasound. Four patients' tumors were reported on third trimester imaging; data regarding the results of ultrasounds performed mid-gestation are not available for these patients. Finally, two patients had normal second trimester ultrasounds and were diagnosed with congenital tumors, a high-grade glioma (tumor# 2) and ATRT (tumor# 44), shortly after birth and at 1 month of life, respectively.

Of the 57 tumors that presented after birth, the most common symptoms at presentation were increased head circumference (24.6%), bulging fontanelle (17.5%), somnolence (8.8%), vomiting (8.8%), apnea (7.0%) and focal neurologic deficits (7.0%). Other presenting symptoms included seizures (5.3%) and hypotonia (1.8%). In three instances, the brain tumor was diagnosed incidentally, two at autopsy (brain involvement by acute myeloid leukemia, tumors #62

Table 1. Clinical, histologic and outcome data for all congenital brain tumors. Abbreviations: AA = anaplastic astrocytoma; aCPP = atypical choroid plexus papilloma; AML = acute myeloid leukemia; ATRT = atypical teratoid rhabdoid tumor; cnLOH = copy neutral loss of heterozygosity; CPC = choroid plexus carcinoma; CPP = choroid plexus papilloma; DA = diffuse astrocytoma; DIGG = desmoplastic infantile ganglioglioma; D/N = desmoplastic/nodular; F = female; GG = ganglioglioma; GBM = glioblastoma; HGG = high-grade glioma; IT = infratentorial; M = male; NEC = not elsewhere classified; NGS = next generation sequencing; PA = pilocytic astrocytoma; SC = spinal cord; SNP = single nucleotide polymorphism microarray; ST = supratentorial; – = no data available.

Tumor	Sex	Age at presentation (months)	Clinical symptoms	Tumor location	Age at surgery/ autopsy	Diagnosis	Molecular findings	Outcome
High-grade gliomas								
1	F	Prenatal	–	ST	3	GBM	*ETV6-NTRK3* fusion (NGS)	Deceased (3 months)
2	F	0	Megalencephaly	ST	0	GBM	*PPP1CB - ALK* fusion, amplification of partial chromosome 2p (NGS)	Deceased (1 day)
3	F	0	–	ST	1	AA	–	–
4	F	0	No respiratory effort at birth	IT	2	GBM	–	Deceased (2 months)
5[§]	F	0	Apnea	ST	3	GBM	–	Deceased (4 months)
6[§]	F	0	Apnea	ST	4	GBM	–	Deceased (4 months)
7	F	2	Seizure	ST	4	AA	–	–
8	F	5	Seizure	ST	5	HGG, NEC	*TRIM24-MET* fusion, gain of chromosome 7 (NGS)[†]	Alive (3 years)[†]
9	F	5	Increasing head circumference	ST	5	HGG, NEC	*EML4-ALK* fusion (NGS)	Alive (1.25 years)
10	F	–	–	–	2	GBM	–	–
11	F	–	–	ST	5	AA	–	–
Low-grade gliomas								
12	F	0	Increasing head circumference	IT	3	PA	–	Alive (20 years)
13	F	0	–	SC	3	PA	–	Alive (6 years)
14	F	0	Apnea	ST	4	Glioma, NEC	–	Alive (12 years)
15	F	3	Eye deviation	ST	3	DA	–	Alive (10 years)
16	F	4	Lethargy, nystagmus and bulging fontanelle	ST	4	PA	–	Alive (11 years)
17	F	4	Ptosis	ST	5	PA	–	Alive (7 years)
18	F	–	Full fontanelle	ST	5	Glioma, NEC	–	–
19	F	–	–	ST	5	PA	–	Alive (16 years)
Ependymomas								
20	F	Prenatal	–	ST	1	Anaplastic ependymoma	*YAP1-MAML2* fusion (NGS)	Deceased (7 weeks)
21	M	2	Hypotonia	SC	2	Anaplastic ependymoma	–	–
22	F	4	Seizure	IT	4	Ependymoma	No clinically relevant findings identified (NGS)	Alive (1.5 years)
Glioneuronal tumors								
23	F	Prenatal	–	ST	2	GG	–	Alive (17 years)
24	F	0	Macrocephaly	ST	5	DIGG	–	Alive (14 years)
25	M	–	–	ST	5	DIGG	–	–

(Continues)

Table 1. (Continued)

Tumor	Sex	Age at presentation (months)	Clinical symptoms	Tumor location	Age at surgery/ autopsy	Diagnosis	Molecular findings	Outcome
26	M	–	–	ST	2	DIGG	–	–
Choroid plexus tumors								
27	F	Prenatal	–	ST	0	CPP	Loss of partial chromosome 1p, and gains of whole chromosomes 2, 7, 12, 13 (NGS)	Alive (3 years)
28	M	0	Vomiting	ST	2	aCPP	–	Alive (10 years)
29	F	2	Lethargy	ST	3	CPP	–	Alive (6 years)
30	M	3	Increasing head circumference	ST	3	CPP	–	Alive (2 years)
31	M	5	–	ST	5	CPC	–	Deceased (22 months)
32	F	5	Vomiting, lethargy	ST	5	CPP	–	–
33	F	5	Increasing head circumference	ST	5	CPP	–	Alive (5 years)
34	M	–	Vomiting and full fontanelles	ST	5	CPC	–	Deceased (10 months)
Medulloblastomas								
35	F	Prenatal	–	IT	0	Medulloblastoma, classic	–	Deceased (1 week)
36	M	0	–	IT	0	Medulloblastoma	–	–
37	F	0	Increasing head circumference and bulging fontanelle	IT	1	Medulloblastoma, D/N SHH-activated, *TP53*-wildtype	–	Deceased (6 months)
38	F	0	Increasing head circumference	IT	4	Medulloblastoma, D/N SHH-activated, *TP53*-wildtype	–	Alive (17 years)
39*	F	1	Macrocephaly	IT	3	Medulloblastoma, D/N SHH-activated, *TP53*-wildtype	Loss of chromosome 9 including *PTCH1* (SNP)	Deceased (3 years)
40	F	2	Somnolence	IT	2	Medulloblastoma, classic non-WNT/non-SHH	No clinically relevant findings identified (SNP)	Alive (6 years)
41	F	4	Increasing head circumference	IT	5	Medulloblastoma, D/N SHH-activated, *TP53*-wildtype	–	Alive (12 years)
42	M	–	–	IT	2	Medulloblastoma, D/N	–	–
43	M	–	Increasing head circumference	IT	3	Medulloblastoma, D/N SHH-activated, *TP53*-wildtype	cnLOH of partial chromosome 1q (NGS)	Alive (3 years)
ATRT								
44	M	0	Full fontanelle	IT	1	ATRT	–	Deceased (1 month)
45‡	F	0	Incidental	IT	4	ATRT	Mosaic homozygous deletion of exons 4–6 of *SMARCB1* and cnLOH of chromosome 22 (NGS)	Deceased (8 months)

(Continues)

Table 1. (Continued)

Tumor	Sex	Age at presentation (months)	Clinical symptoms	Tumor location	Age at surgery/ autopsy	Diagnosis	Molecular findings	Outcome
46	M	4	Increasing head circumference	ST	4	ATRT	Loss of one copy of chromosome 22 and a deletion of exon 1 in the remaining copy of *SMARCB1* (NGS)	Alive (1 year)
47	M	5	Vomiting	IT	5	ATRT	–	Deceased (6 months)
48	F	5	Increasing head circumference	ST	5	ATRT	Mosaic homozygous nonsense mutation in exon 5 of *SMARCB1* (NGS)	Deceased (17 months)
49	F	–	–	IT	2	ATRT	–	Deceased (2 months)
50‡	F	–	Macrocephaly	IT	4	ATRT	–	–
51	F	–	–	–	5	ATRT	–	–
Other embryonal tumors								
52	F	Prenatal	–	ST	0	Medulloepithelioma	four copies of chromosomes 2, 7, 8, 11, 14, 18 and 20 and cnLOH of the other chromosomes (NGS)	Deceased (3 months)
53	M	4	Bulging fontanelle	ST	4	Embryonal tumor, NOS	–	Deceased (5 months)
54	M	–	Somnolence	ST	3	Pineoblastoma	–	Deceased (10 months)
Germ cell tumors								
55	M	Prenatal	–	ST	5	Immature teratoma	–	Deceased (5 months)
56	M	0	Bulging fontanelle	ST	0	Immature teratoma	–	Alive (4 years)
57	F	0	–	IT	0	Malignant mixed germ cell tumor	–	–
58	F	0	Bulging fontanelle	ST	4	Immature teratoma	No clinically relevant findings identified (SNP)	–
59	M	0	Bulging fontanelle	ST	4	Mature teratoma	–	Alive (11 years)
60	F	1	Vomiting	IT	1	Mature teratoma	–	Alive (1 year)
61	M	–	–	ST	3	Immature teratoma	–	Alive (4 years)
Other tumors								
62	M	0	Incidental on autopsy	ST	0	AML involving brain	–	Deceased (10 days)
63	F	0	Incidental on autopsy	ST	0	AML involving brain	–	Deceased (16 days)
64	M	0	Bulging fontanelle	ST	1	Malignant glioneuronal tumor, NEC	No clinically relevant findings identified (SNP)	Deceased (4 years)
65	F	0	Unilateral facial droop	IT	4	Juvenile xanthogranuloma	–	Alive (4 years)

*Patient has Gorlin syndrome.

†Patient had radiographic evidence of progression at 2 year of age and was resected again at age 2. Next generation sequencing was performed on the second resection.

‡Patient has rhabdoid tumor predisposition syndrome.

§Same patient; tumors five and six came from the same patient.

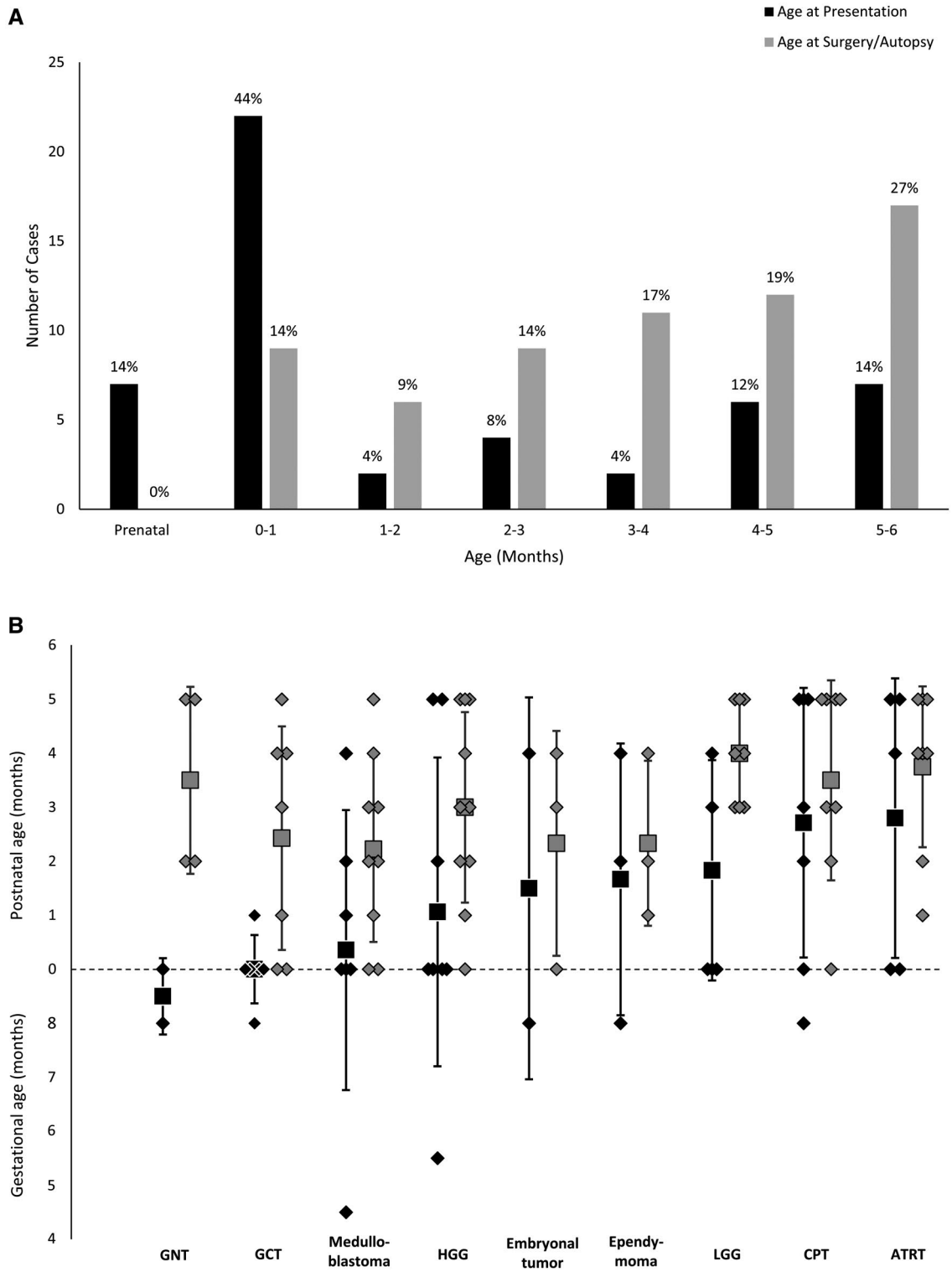

Figure 1. *Age at presentation and surgical resection/autopsy*. A. Histogram of the age at clinical presentation (black bars) in comparison to the age at surgery/autopsy (gray bars) across all tumor types. B. Histogram of the age at clinical presentation (black) vs. age at surgery/autopsy (gray) for each tumor type. Diamonds represent individual tumors and squares represent the mean for each group. Error bars represent standard deviation. Abbreviations: ATRT, atypical teratoid rhabdoid tumor; CPT, choroid plexus tumor; GCT, germ cell tumor; GNT, glioneuronal tumor; HGG, high-grade glioma; LGG, low-grade glioma

and #63) and one on full body imaging in the setting of a child with a tumor predisposition syndrome (tumor #45).

Outcome data were available for 49 of the 64 (77%) patients (Table 1 and Figure 2). Twenty-two patients (45%) were deceased at the conclusion of this study with an average survival of 8.93 ± 13.2 months (range 1 day–s4.5 years) following premortem diagnosis (two subjects' tumors were incidentally diagnosed upon autopsy). Twenty-seven patients (55%) were alive at the conclusion of this study with an average follow-up of 7.77 ± 5.60 years (range 1–20 years). All patients with low-grade gliomas and glioneuronal tumors were alive at the conclusion of the study. In contrast, the majority of patients with high-grade gliomas and ATRTs and all patients with other embryonal tumors were deceased. When tumors with assigned WHO grades were grouped by grade, all patients with WHO grade I (N = 11) and WHO grade II (N = 3) tumors were alive at the conclusion of the study. In contrast, only 25% of infants with WHO grade III tumors (N = 4) and 25% with WHO grade IV tumors (N = 20) were alive at the study conclusion (Figure 2A). Medulloblastomas were the WHO grade IV tumor with the best outcome with 57% of patients still living at the conclusion of the study (Figure 2B).

The majority of the congenital CNS tumors were able to be classified using the 2016 WHO classification of CNS tumors. For these tumors, the molecular findings supported the histologic diagnosis when available (eg, homozygous deletions in *SMARCB1*/*INI1* in ATRTs). Five tumors could not be classified using the current WHO criteria (tumors # 8, 11, 14, 18 and 64), and tumors #1 and #20 were only able to be classified following molecular testing. The histologic findings of tumor #14 have been previously published (30) (patient #1). Of all the congenital CNS tumors, the high-grade gliomas were often the most difficult to classify and required integration of histologic, immunohistochemical and molecular information. The following are three examples of high-grade gliomas which were histologically difficult to classify in the absence of molecular findings.

Example Case 1 (Tumor #1)

Tumor #1 was diagnosed on prenatal ultrasound in a 26 weeks gestation female and was initially thought to be a large vascular malformation within the left cerebral hemisphere. The infant was delivered at 27 weeks gestation and remained in the intensive care unit due to high output cardiac failure and respiratory failure. Her head circumference increased rapidly over the first months of life and an MRI showed compression and cystic changes of the right hemisphere with minimal normal brain parenchyma. She expired at 3 months of age at which point an autopsy was performed. Postmortem examination revealed replacement of the left cerebral hemisphere by a hemorrhagic and necrotic red-brown mass (Figure 3A,B). Histologic examination showed a highly vascular tumor with regions of necrosis (Figure 3C–E) which was positive for vimentin and OLIG2, with only focal GFAP staining (Figure 3F). The tumor cells were negative for the following stains: synaptophysin, CD45, TdT, desmin, myoD1, myogenin, OCT4, HMB45, SOX-10, cytokeratin, transthyretin, EMA, CD31, CD34, INI1 (retained) and BRG1 (retained). NGS revealed the presence of an *ETV6-NTRK3* fusion. While the *ETV6-NTRK3* fusion is also present in infantile fibrosarcomas, this diagnosis was ruled out both by histology and immunohistochemistry and the tumor was classified as a glioblastoma, *IDH*-wildtype, WHO grade IV.

Example Case 2 (Tumor #8)

Tumor #8 was diagnosed in a five-month-old female who presented with seizures. She was found to have a large mass arising from the deep white matter of the posterior left frontal lobe, with extension into the left lateral ventricle and underwent subtotal resection at 5 months. Histologically, the tumor was relatively well circumscribed, and areas of infiltration were not observed. Calcifications were present throughout the tumor (Figure 4A). The tumor was composed of small to medium sized glial cells within a myxoid background and scattered mitoses were present (Figure 4B). The tumor cells were positive for GFAP and the Ki-67 proliferation index was up to 10% (Figure 4C,D). Staining for neuronal markers was negative, and the tumor was classified as a high-grade glioma. Follow-up imaging revealed a small, residual nodule and the patient was treated with chemotherapy. At age two, the tumor progressed and was resected again. The recurrence was histologically identical to the initial resection. Molecular testing performed on the recurrent/residual tumor revealed a *TRIM24-MET* fusion. The patient remains progression free 1 year following the second resection.

Example Case 3 (Tumor #9)

Tumor #9 was received in consultation. The specimen was from a five-month-old female who presented with increasing head circumference and was found to have a large hemispheric mass. Histologically, the tumor was composed of sheets of mitotically active tumor cells which demonstrated focal GFAP positivity (Figure 5A,C). A few pale nodules were also present within the tumor which stained for neurofilament, indicating neuronal differentiation (Figure 5B,D). NGS revealed the presence of an *EML4-ALK* fusion. In light of the molecular findings, this tumor was classified as a high-grade glioma (9, 22). The patient was treated with chemotherapy and was found to have no residual disease on MRI at 15 months after resection.

DISCUSSION

Congenital CNS tumors are generally thought to represent 0.5%–1.9% of all pediatric CNS neoplasms though rates of up to 4% have been reported (14, 23). At our institution, congenital CNS tumors accounted for 2.0% of all CNS neoplasms, consistent with prior studies (Table 2). The variance in rates is likely in part due to the inconsistent criteria used to diagnose congenital CNS tumors with inclusion criteria ranging from patients aged less than 4 weeks up

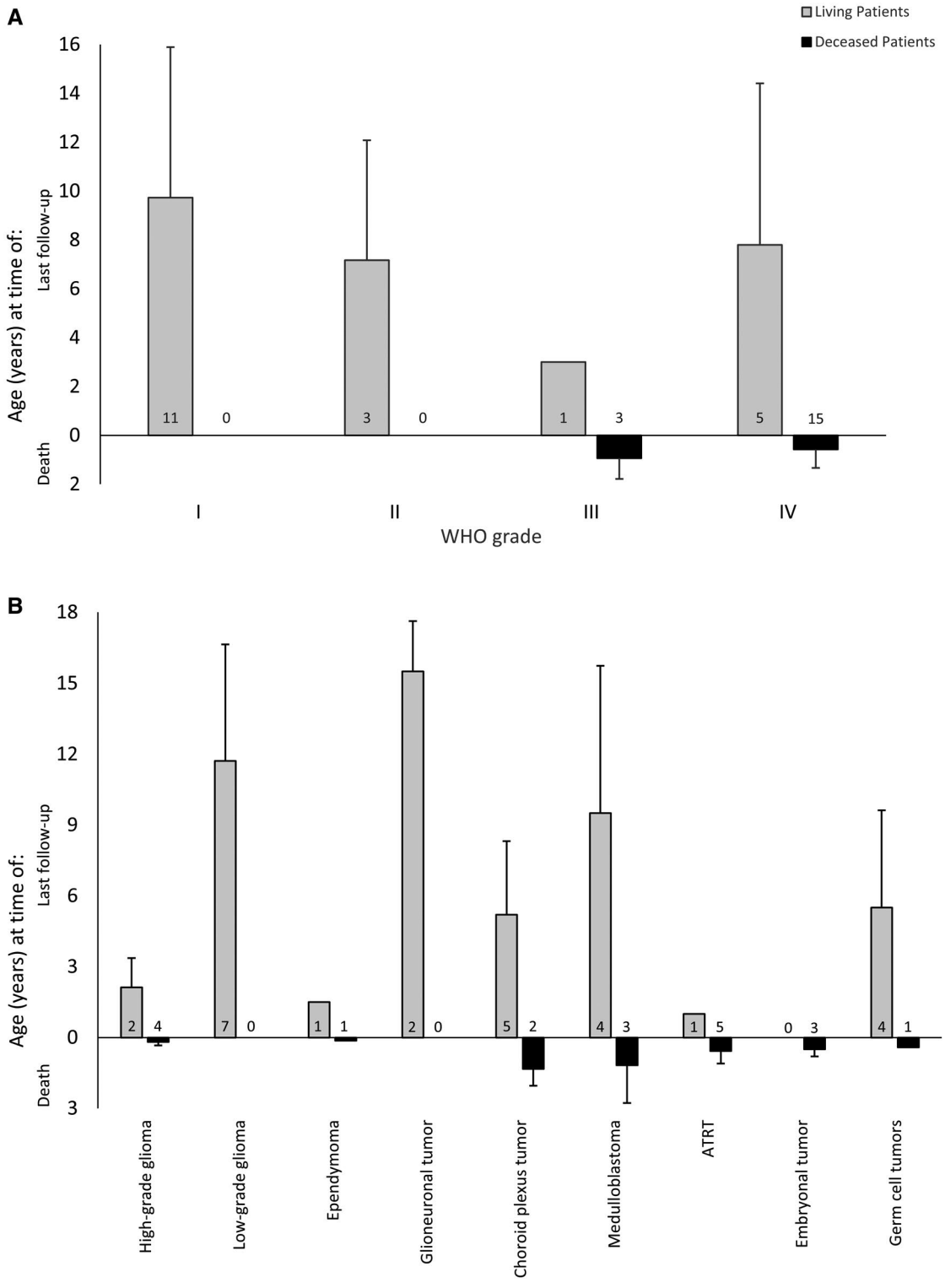

Figure 2. *Outcome data.* A. Age at the time of last follow-up for surviving patients (gray bars) and age at the time of death (black bars) for tumors with assigned WHO grades. Error bars represent standard deviation. Labels indicate the N for each group. **B.** Age at time of last follow-up for surviving patients (gray bars) and age at the time of death (black bars) by tumor type. Error bars represent standard deviation. Labels indicate the N for each group. Abbreviations: ATRT, atypical teratoid rhabdoid tumor

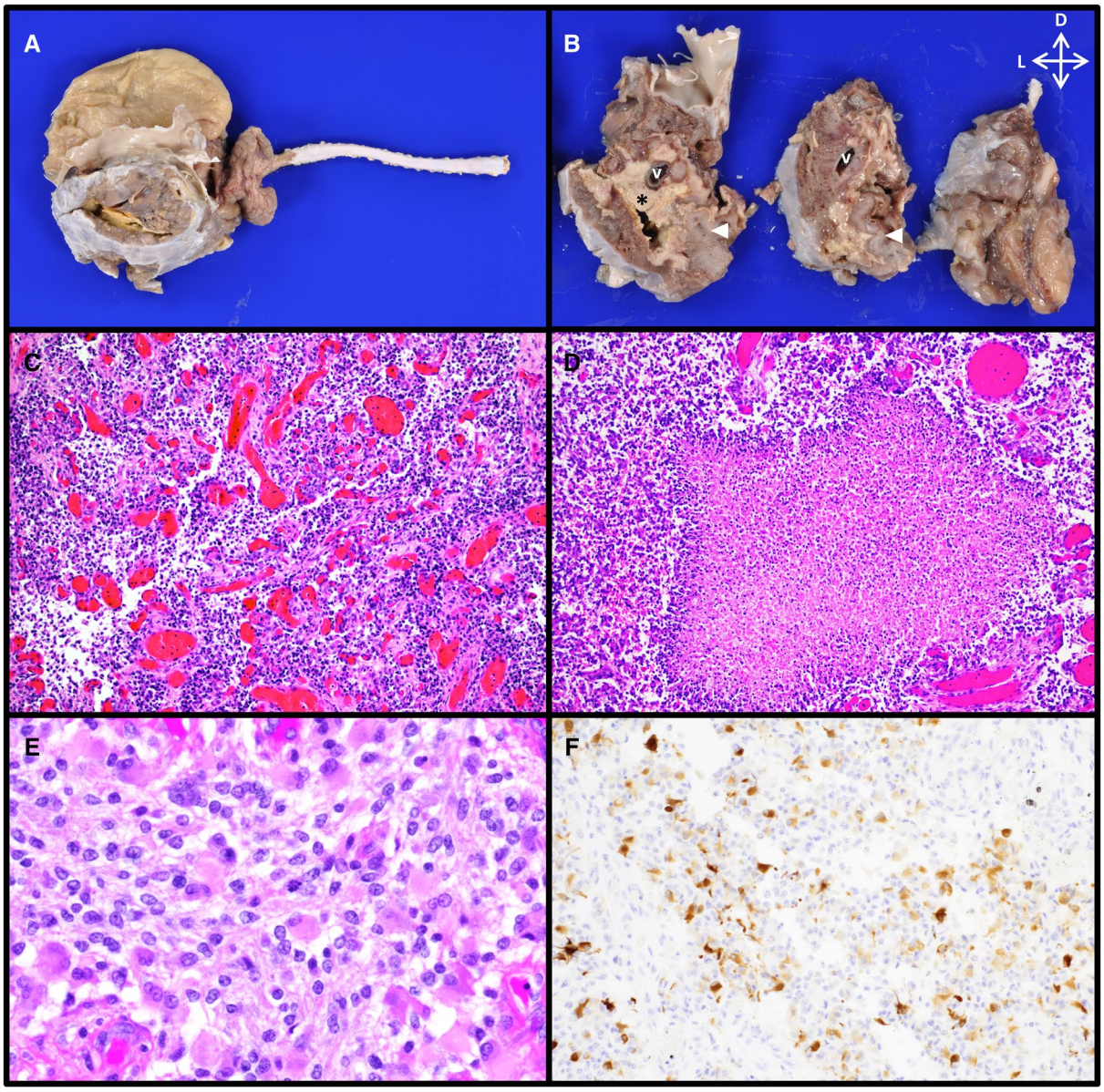

Figure 3. *Gross and microscopic appearance of Tumor #1.* **A.** Upon autopsy examination, the left cerebrum was completely replaced by a firm, vascular, reddish-brown mass, attached medially to the superior sagittal sinus. On the right, the cerebrum was composed of a large, cystic cavity with translucent thin cortical mantle. **B.** Coronal sections of the left hemisphere demonstrated a large, reddish-brown firm mass with enlarged vascular spaces (v). The central portion was composed of yellow, disintegrating necrotic tissue (asterisk). Minimal residual cortex could be identified (white arrowheads). The legend indicates lateral (L) and dorsal (D) for each coronal slice. **C.** The tumor was highly cellular and vascular (hematoxylin and eosin stain, 100x magnification). **D.** Regions of palisading necrosis were present within the tumor (hematoxylin and eosin stain, 100x). **E.** Tumor nuclei were round to ovoid. Occasional multinucleated tumor cells were present as were cells with eosinophilic cytoplasm and eccentrically located nuclei (hematoxylin and eosin stain, 400x). **F.** Staining for GFAP demonstrated focal, patchy positivity (GFAP immunostain, 200x magnification) [Colour figure can be viewed at wileyonlinelibrary.com]

to patients under 1 year old (2, 6, 8, 17–20, 29, 32, 34, 36). Our percentage is likely at the higher end of the range as we included tumors in patients up to 6 months old. We chose to perform a database search in patients up to 6 months of age for two reasons. First, we wanted to include tumors that are classified as "probably" congenital in origin (6). Second, many tumors presented clinically several weeks prior to surgical resection or autopsy (Figure 1B). Our database search was based on resection/autopsy dates, and several tumors presenting prior to 2–3 months of age would have been missed in a more restricted database search. The majority of the cases in this study (62%) presented before 2 months of age and by most classification systems would be considered congenital in origin (6, 35, 39). The remaining subjects presented before 6 months of life and could be classified as "probably" congenital in origin (6).

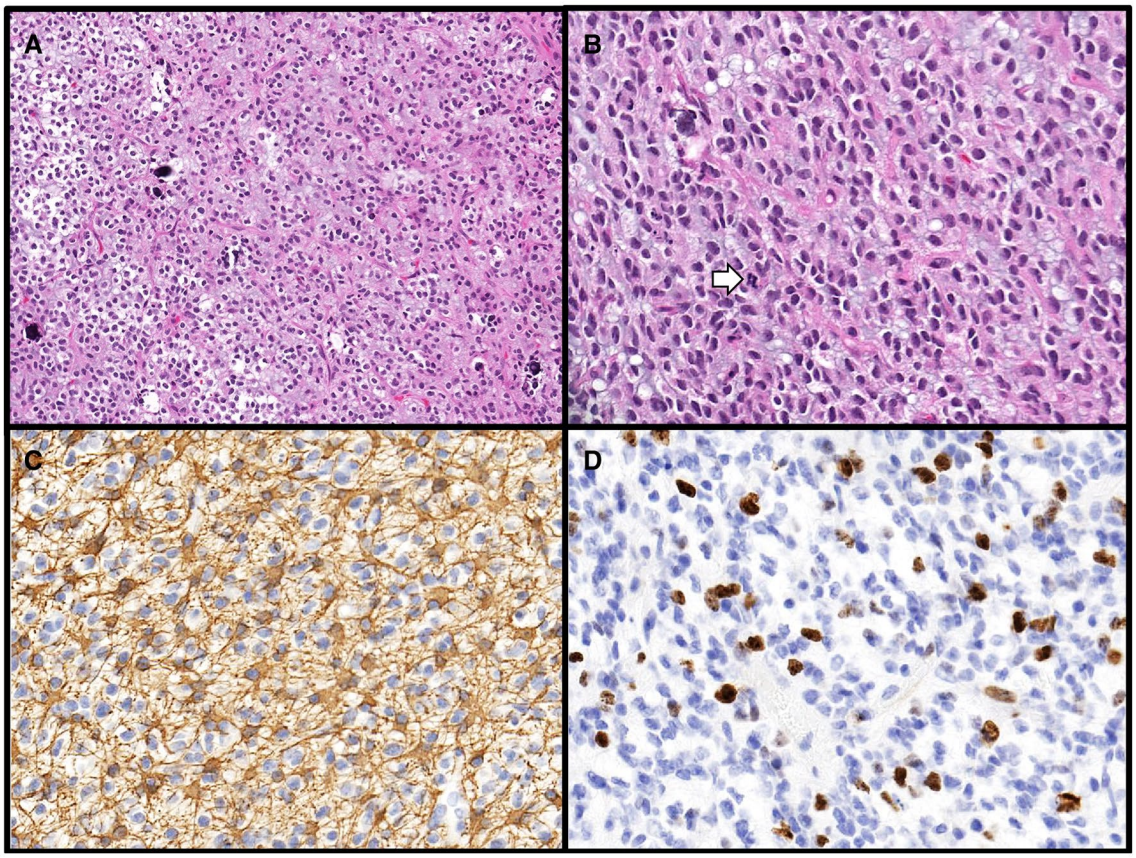

Figure 4. *Histology of Tumor #8.* **A**. The tumor was cellular with a sheet-like growth pattern and scattered calcifications (hematoxylin and eosin stain, 100x magnification). **B**. The tumor cells were small- to medium-sized within a myxoid background. Scattered mitoses were present as highlighted by the white arrow (hematoxylin and eosin stain, 200x magnification). **C**. The tumor cells were positive for GFAP (GFAP immunostain, 200x magnification). **D**. The Ki-67 proliferation index was up to 10% (Ki-67 immunostain, 200x magnification) [Colour figure can be viewed at wileyonlinelibrary.com]

We found a female predominance in our cohort (M:F = 1:2). This is likely secondary to the marked female predominance seen in the most common tumor types: medulloblastomas and low- and high-grade gliomas. Other tumor types had male-to-female ratios closer to 1:1. In the literature, the male-to-female ratios reported for congenital CNS tumors are closer to 1:1 (2, 17, 20). The significance of the female predominance is unclear, especially in the setting of prior studies showing no gender differences (20) or even a slight male predominance in congenital CNS tumors (Table 2) and in some pediatric brain neoplasms (2, 18, 37).

Three patients in this study (5% of patients) were diagnosed with a congenital CNS tumor in the setting of a tumor predisposition syndrome. One patient with Gorlin syndrome was found to have a medulloblastoma (tumor #39). Two patients with rhabdoid tumor predisposition syndrome were diagnosed with ATRTs (tumors #45 and 50).

A literature review had found up to 12% of congenital brain tumors were diagnosed on prenatal imaging (12) and our frequency of 14% is consistent with that (Table 2); there was no correlation between tumor type and prenatal diagnosis. Increased head circumference was the most common presentation of tumors diagnosed after birth in our cohort, independent of tumor type (12, 20). Bulging fontanelle was another very common clinical presentation. Similar findings have been reported in the literature; macrocephaly, hydrocephalus and other signs of increased intracranial pressure are the most common presenting signs (12, 15, 20, 24, 31, 33, 43). This is in contrast to brain tumors in older children which most commonly present with headache, vomiting and behavioral problems (41).

At the conclusion of this study, just over half of the patients with follow-up data (55%) were alive. An extensive review of congenital brain tumors from 2002 found these tumors to have an overall poor prognosis with an overall survival of only 28% (13). However, with advancements in therapy, better outcomes have been reported in recent years as summarized in Table 2 (17, 20, 22, 24, 31, 33, 43). Not unexpectedly, we found that higher-grade tumors are associated with higher mortality rates (75% and 67% for WHO grade III and grade IV tumors, respectively) than low-grade neoplasms. WHO grade I and grade II tumors in our cohort had a 100% survival rate and many of these cases had several years of follow-up.

Mirroring prior studies the majority (64%) of the congenital CNS tumors in our study were supratentorial (2, 3, 12, 32). This is one of the many ways these tumors differ from those in older children which are often located in the

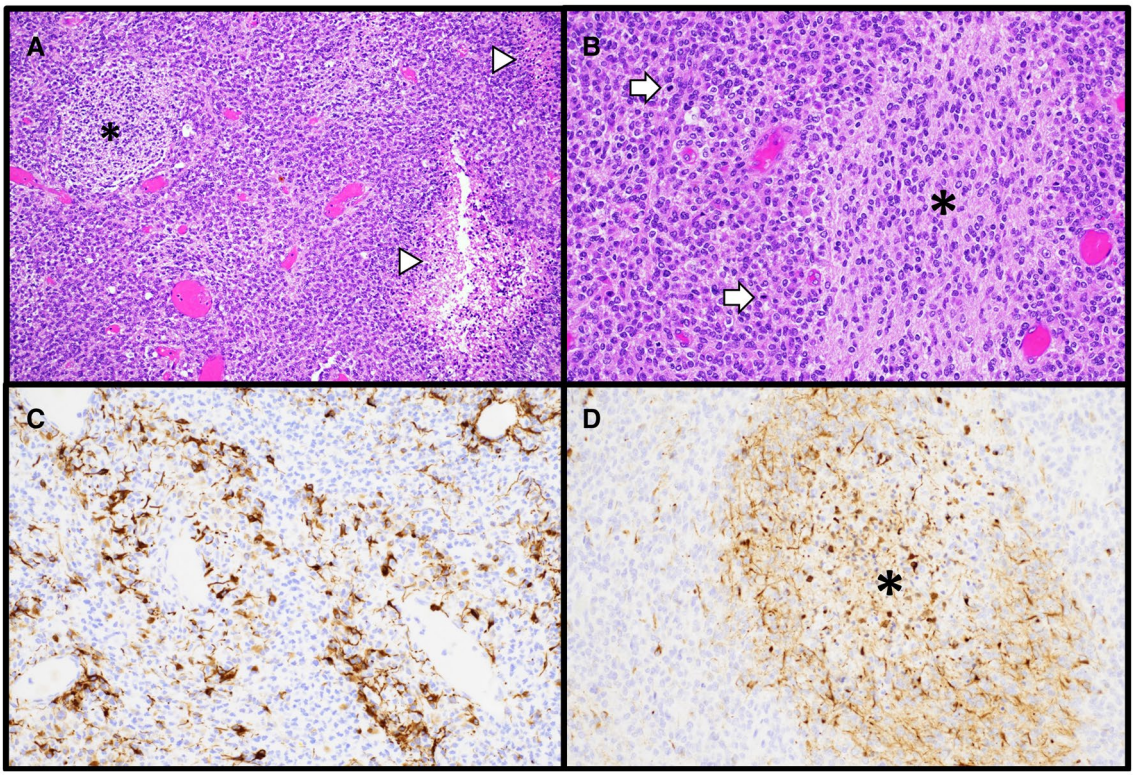

Figure 5. *Histology of Tumor #9.* A. At lower magnification, the tumor was highly cellular and demonstrated sheet-like growth with regions of palisading necrosis as indicated by the white arrowheads and pale islands as indicated by the black asterisk (hematoxylin and eosin stain, 100x magnification). B. Within highly cellular regions, mitoses were frequent (white arrows). The pale islands (black asterisk) were less cellular and contained a neuropil background (hematoxylin and eosin stain, 200x magnification). c. The tumor demonstrated patchy positivity for GFAP within cellular regions (GFAP immunostain, 200x magnification). D. Immunostaining for neurofilament highlighted the pale islands designated by the black asterisk (neurofilament immunostain, 200x magnification) [Colour figure can be viewed at wileyonlinelibrary.com]

posterior fossa. Similarly, teratomas and choroid plexus tumors are associated with neonates and infants rather than older children (12). While pilocytic astrocytomas, malignant gliomas and medulloblastomas are the most common brain tumors in children under 14 years of age (28, 40), teratomas/germ cell tumors are generally regarded to be the most common congenital CNS entities (2, 3, 12, 26, 32, 36) though in some studies glial tumors comprised the largest subset (2, 15, 17, 20, 24, 31, 43). In our study, germ cell tumors accounted for 11% of all congenital CNS tumors, and high-grade gliomas were the most common tumor type (16% of all tumors).

It is likely that the frequencies of the various types of congenital CNS tumors will change as the classification of brain tumors evolves with the integration of molecular data. For example, neoplasms previously classified as supratentorial primitive neuroectodermal tumors are now classified as either high-grade gliomas or embryonal tumors.

Indeed, we found molecular information to be essential for accurate classification of a subset of our cases. While the majority were easily classified, a subset of the tumors had unique histologic features that did not fit well into a clearly defined WHO category. In some of these tumors, particularly the high-grade gliomas, molecular information aided classification. For example, for tumors #1, 8 and 9 described above, the molecular findings helped to firmly place them in the high-grade glioma category. Interestingly, the molecular findings in the high-grade glioma subgroup of congenital CNS tumors are distinct from the molecular characteristic of high-grade gliomas in older children and adults. *ALK* fusions are associated with histologically difficult to classify gliomas in infants less than a year old (1,27). These gliomas are often large, hemispheric masses with cystic spaces on imaging (27). Multiple *ALK* fusion partners have been identified in the literature including both genes identified in our cohort, *PPP1CB* and *EML4* (9, 25). Fusions involving *ALK* are often seen in gliomas of infancy but rarely in older children and adults (4, 8, 9).

Similarly, fusions involving the *MET* oncogene have been described in up to 10% of pediatric high-grade gliomas and 3%–7% of pediatric glioblastomas (9, 11). The same fusion described in this study (*TRIM24-MET*, tumor #8) has been reported in a neonatal brain tumor (10). Given a lack of radiographic and histologic evidence of infiltration for tumor #8, we chose to classify this as a high-grade glioma rather than an anaplastic astrocytoma.

NTRK fusions have been reported in up to 40% of hemispheric high-grade gliomas in children under 3 years of age (42) and are commonly found in infantile high-grade gliomas (4, 9). The specific *ETV6-NTRK3* fusion seen in

Table 2. Summary of findings from larger reviews and case series of congenital and infantile central nervous system tumors. Abbreviations: CPT = choroid plexus tumors; IT = infratentorial; N/A = not applicable; PNET = primitive neuroectodermal tumors; SC = spinal cord; ST = supratentorial; – = data not available.

Study	Number of cases	% of all pediatric brain tumors	Patient ages at diagnosis	M:F	Tumors	Tumor location	Common initial clinical presentations	% of cases diagnosed prenatally	Outcomes
Isaacs, 2002 (12, 13)	250*	–	Includes studies of patients up to 12 months	–	Teratomas (30%) Astrocytomas (19%) PNET (13%) CPT (13%)	ST (>60%)	Macrocephaly (29%) Hydrocephalus (17%) Stillborn (10%)	12.2%	28% survival rate
Young and Johnston, 2004 (43)	16	5.6%	Prenatal-12 months	1.7:1	Low-grade gliomas (44%) Glioneuronal tumors (19%) High-grade gliomas (13%)	ST (62%) IT (38%)	Increasing head circumference (38%) Vomiting (31%) Lethargy (31%) Failure to thrive (31%)	12.5%	75% survival rate (follow-up range 12–129 months)
Lasky *et al* 2007 (20)	12	–	Prenatal-6 months	1:1	Gliomas (50%) Medulloblastoma (17%) Germ cell tumors (17%)	ST (42%) IT (33%) ST/IT (25%)	Increased head circumference (75%) Ocular symptoms (25%)	8.3%	58% survival rate (follow-up range 6–120 months)
Cassart *et al* 2008 (3)	27	–	Prenatal	–	Germ cell tumors (56%) Gliomas (15%) Craniopharyngiomas (7%)	ST (96%) IT (4%)	All tumors diagnosed on prenatal ultrasound	N/A	–
Mehrotra *et al* 2009 (24)	18	4.8%	Prenatal-12 months	1.6:1	Gliomas (44%) PNET (22%) CPT (11%)	ST (67%) IT (33%)	Increased intracranial pressure (61%) Increasing head circumference (57%) Seizures (50%)	5.6%	44% survival rate (follow-up range 9–28 years)
Shamji *et al* 2009 (33)	13	<2%	Prenatal-12 weeks	2.3:1	Embryonal tumors (62%) CPT (23%)	ST (39%) IT (46%) SC (15%)	Hydrocephalus (69%) Increasing head circumference (28%) Hypotonic (30%)	7.7%	38% survival rate (follow-up range 8 months–9 years)
Serowka *et al* 2010 (31)	33	–	Prentatal-6 months	1.8:1	Gliomas (33%) CPT (28%) Embryonal tumors (24%)	ST (64%) IT (21%) ST/IT (15%)	Hydrocephalus (55%) Increased intracranial pressure (55%) Eye findings (52%)	6.1%	42% survival rate (Follow-up range 2–21 years)

(Continues)

Table 2. (Continued)

Study	Number of cases	% of all pediatric brain tumors	Patient ages at diagnosis	M:F	Tumors	Tumor location	Common initial clinical presentations	% of cases diagnosed prenatally	Outcomes
Jaing *et al*, 2011 (15)	22	–	Prenatal-12 months	4.5:1	Gliomas (32%)	ST (55%)	Increased head circumference (23%)	4.5%	73% survival rate (follow-up range 1 month–14 years)
					Medulloblastomas (18%)	IT (45%)	Seizure (23%)		
					CPT (14%)		Vomiting (18%)		
Jurkiewicz *et al* 2012 (17)	56	–	Prenatal-12 months	1.5:1	Gliomas (32%)	ST (68%)	–	7.1%	66% survival rate (follow-up range 1–115 months)
					Embryonal tumors (27%)	IT (32%)			
					CPT (21%)				
Current Study	64	2.0%	Prenatal-6 months	1:2	High-grade gliomas (16%)	ST (63%)	Increased head circumference (25%)	14.0%	55% survival rate (follow-up range 1–20 years)
					Medulloblastomas (14%)	IT (34%)	Bulging fontanelle (18%)		
					Low-grade gliomas (12%)	SC (3%)	Somnolence (9%)		

*Represents a large review of the literature on congenital brain tumors prior to 2002.

tumor #1 has been reported in a glioblastoma in a one-month-old infant (42).

Fusions involving the above genes are associated with gliomas of young pediatric patients in addition to fusions in *ROS1* and alterations in the MAPK pathway (4, 8, 9). These molecular findings are distinct from the molecular alterations seen in high-grade gliomas of older children and adults. Mutations in histone genes (such as H3K27M and H3G34R/V) associated with high-grade gliomas in older children were not detected in this cohort of congenital CNS tumors. Additionally, genetic alterations commonly seen in adult gliomas involving genes such as *IDH1/2* and *EGFR* were not detected. While this study only includes molecular testing in four congenital high-grade gliomas, our findings mirror what has been reported for infantile high-grade gliomas and supports the notion that these congenital CNS tumors are molecularly distinct from older pediatric and adult gliomas, often containing solitary alterations that may be candidates for targeted therapies (4, 8, 9, 18).

The 64 tumors in this study illustrate the wide spectrum of congenital CNS tumors. These tumors are distinct from brain tumors of older pediatric patients in several ways including location, presenting symptoms, histologic subtypes and molecular characteristics. Our findings support the notion that these tumors, particularly high-grade gliomas, should be treated as a distinct subgroup of brain tumors. Follow-up data show that outcomes, particularly for patients with low-grade tumors, have improved over time with advancements in diagnosis and treatment. Additional, larger studies are needed to fully characterize these rare CNS tumors and better understand their unique characteristics.

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CONFLICTS OF INTEREST

None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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