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Characterization, treatment, and outcome of intracranial neoplasms in the first 120 days of life

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Abstract

Little is known about brain tumors in early infancy. We reviewed the records of 27 patients (12 boys and 15 girls) diagnosed within 120 days of birth. The median age was 66 days (range, 0–110 days) at diagnosis. All patients underwent surgery; 18 received adjuvant chemotherapy, and 3 received adjuvant chemotherapy and radiation therapy. The median follow-up was 2.1 years (range, 0.2–21.6 years). At last encounter, 15 patients were alive, and 11 had no evidence of disease. Ten patients died of progressive disease, and 2 died of treatment-related complications. All survivors experienced late effects, including endocrine, neurologic, and cognitive deficits. Of the 13 patients who completed neurocognitive assessments, 7 had an IQ score less than 70. Children in whom brain tumors arise during early infancy can be cured with conventional therapy; however, contemporary approaches can adversely affect long-term function, and families need to be aware when making therapeutic decisions.

Keywords

neonatal; congenital; early infancy; brain tumors

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Author Contributions

Ibrahim Qaddoumi and Amar Gajjar thought of the concept. Ibrahim Qaddoumi and Steven Carey collected the data and wrote the first draft. All other coauthors contributed to the data interpretation, and subsequent draft.

Declaration of Conflicting Interests

The authors declare have no financial or other conflicting interests with respect to this article.

Introduction

The contribution of age at the time of cancer diagnosis to a child's prognosis and quality of life is a well-known phenomenon that differs based on the diagnosis. Children with neuroblastoma diagnosed at or before 1 year of age fare well with minimal therapy¹; the same age group with leukemia fares worse than children who are older at diagnosis.² Furthermore, finer analysis of the infant groups in leukemia and neuroblastoma has revealed that the outcome of patients younger than 6 months with newly diagnosed leukemia is substantially worse than that of infants who are older than 6 months at diagnosis.^{2,3} Patients with metastatic neuroblastoma diagnosed during the first 2 months of life also have worse outcomes than those who are older than 2 months at diagnosis.⁴

The effect of age on the prognosis for infants and young children with brain tumors depends on the histology of the tumor.⁵⁻⁹ Patients with high-grade glioma^{6,8} or diffuse pontine glioma^{5,8} early in life have better overall survival than their older counterparts, whereas those with low-grade glioma^{7,8} or embryonal tumor⁹ have inferior overall survival. Historically, our clinical trials for infants and children with brain tumors have included children 3 years or younger⁹⁻¹⁴; therefore, little information is available about the specific clinical characteristics, survival, and late effects of those with cancer diagnosed in the first few months of life. This information may serve to advance treatment, educate healthcare providers, and improve monitoring and rehabilitation efforts. Therefore, here we present data on treatment and outcome for infants with intracranial neoplasms during the first 120 days of life at our institution.

Patients and Methods

After obtaining approval from the St. Jude Children's Research Hospital's institutional review board, we conducted a retrospective review of the medical records of patients with brain tumors who were referred to St. Jude Children's Research Hospital within the first 120 days of life. Date of diagnosis was designated as the date of the first radiologic scan showing a tumor. The period examined was from January 1985 to December 2008, and 27 patients met these inclusion criteria.

Initial clinical, radiologic, and histopathologic findings, therapeutic interventions, survival data, and late effects were reviewed. The extent of tumor resection was determined by reviewing the operative report and the immediate postoperative scans. Gross total resection was defined as no visible tumor remaining, near total resection as removal of more than 90% but less than 100% of tumor, subtotal resection as removal of 50% to 90% of the tumor, partial resection as removal of 10% to 49% of the tumor, and biopsy as removal of less than 10%. All tumor samples were reviewed by a neuropathologist prior to initiating therapy.

Among the 27 patients included in this study, 13 (48%) participated in neurocognitive assessments as part of protocol-based monitoring or clinical follow-up. For individuals with multiple assessments, the most recent assessment was used to best characterize long-term cognitive outcomes. The assessments of all 13 patients included an index of intellectual functioning (i.e., intelligence quotient, IQ) derived from measures standardized on large representative normative samples that have demonstrated reliability and validity.¹⁵⁻²⁰ Eleven assessments also included the Vineland Adaptive Behavior Scale,²¹ which measures adaptive functioning on the basis of a parental interview. All IQ and Vineland Adaptive Behavior Scale scores were age standardized with a mean of 100 and standard deviation of 15. Six assessments included the Achenbach Child Behavior Checklist,²² which is a parental rating of behavioral problems and social competencies. Scores for clinical scales of this measure were age standardized with a mean of 50 and standard deviation of 10.

RESULTS

Patient and clinical characteristics

During the study period, 1819 patients with primary diagnoses of central nervous system malignancy were referred to the Brain Tumor Program at St. Jude. Of those, 27 (1.5%) met the criteria for our study. The median age at diagnosis was 66 days (range, 0–110 days). The clinical and demographic features of the study cohort are summarized in Table 1.

The most common histopathologic characteristics were gliomas (n=11) and embryonal tumors (n=9) (Table 2). Thirteen (48%) tumors were in the supratentorial compartment, and 14 (52%) were in the infratentorial compartment. All embryonal neoplasms were infratentorial, whereas the astrocytomas were evenly distributed.

Treatment

Three main modalities were used to treat these patients: surgical resection, chemotherapy, and radiation therapy (Table 2). At diagnosis, all patients underwent surgery. After definitive surgery, adjuvant chemotherapy was administered to 18 patients, and a combination of adjuvant chemotherapy and radiation therapy was administered to 3 patients.

Twenty (74%) patients experienced relapse: 11 cases were confined to the primary tumor site, and 9 were associated with disseminated disease. At recurrence of disease, the treatment approach varied according to tumor histology and extent of relapse as summarized in Table 2. Seven patients experienced multiple recurrences (median, 2; range, 2–6).

The cumulative treatment burden was substantial in our cohort. Eighteen patients required placement of a ventriculoperitoneal shunt: 11 required shunt revisions (median number of revisions per patient, 1; range, 1–3). Chemotherapy was administered to 23 patients. The median number of chemotherapy cycles administered per patient was 9 (range, 1–34). Of the patients who received chemotherapy, 11 (48%) required a median of 2 regimens (range, 2–7). Notably, radiation therapy was administered to 9 patients; in 3, radiation therapy was used as adjuvant therapy; in 6 others, it was used upon disease recurrence. One patient received radiation therapy only for palliation. The median age at the initiation of radiation therapy was 1.8 years (range, 1.0–5.4 years).

Survival

The median follow-up in this study was 2.1 years (range, 0.2–21.6 years). At the time of the study, 12 (44%) patients had died: 10 died of disease; 2 died of treatment-related sequelae (1 of aspiration pneumonia secondary to postoperative vocal cord paralysis and 1 of viral pneumonia). Fifteen (56%) patients were alive, and 7 had experienced no recurrence. Pathologic features of the tumors from the surviving patients included 8 gliomas (3 pilocytic astrocytomas, 2 fibrillary astrocytomas, 1 high-grade glioma, 1 mixed glioneuronal tumor, and 1 desmoplastic infantile ganglioglioma with high-grade component). Histology of tumors from the remaining 7 survivors included 3 ependymomas, 3 choroid plexus tumors, and 1 medulloblastoma.

The pathology from the 7 patients who had not experienced recurrence of disease included 2 choroid plexus carcinomas and 1 each of desmoplastic infantile ganglioglioma, mixed glioneuronal tumor, fibrillary astrocytoma, high-grade glioma, and ependymoma.

Cognitive, neurologic, and endocrine late effects

A substantial number of neurologic, behavioral, and developmental sequelae were observed in this study population after initial treatment, upon relapse, and during longitudinal follow

up. These sequelae included oculovisual (56%) and hearing (48%) deficits and dysphagia (22%). Delayed growth (11%) and delays in motor (85%), intellectual (37%), and speech (48%) development were reported in the majority of patients. Seizure disorders developed in 17 patients; of those, 13 were being actively treated on antiepileptic drugs as of last contact. Endocrine dysfunction developed in 9 patients who required hormone replacement therapy; these regimens included 1 to 4 drugs.

No statistical differences were detected between the group of 13 patients who participated in neurocognitive assessments and those who did not with respect to sex ($\chi^2 = .36$, $p = .55$), age at diagnosis ($t = -.79$, $p = .44$), extent of initial surgical resection ($\chi^2 = .47$, $p = .79$), initial mode of treatment ($\chi^2 = .52$, $p = .77$), or ventriculoperitoneal shunt placement ($\chi^2 = .30$, $p = .59$). The mean age of patients at the time of their most recent assessment was 4.82 ± 3.93 years. There was no difference in IQ scores based on which specific IQ measure was used ($F = 2.44$; $p = .13$); therefore, scores were combined for analysis (Figure 1). The IQ of the group was significantly below the average range of the normative sample (71.31 ± 22.08 ; $t = -4.69$, $p = .001$); 69% had an IQ less than average (i.e., < 85), and 54% had an IQ less than the threshold used to determine mental retardation (i.e., < 70). Five patients had an IQ score ≤ 50 (4 reported scores were ≤ 50 , and 1 was 41). The reported scores of 50 or lower were treated as a score of 50 for the purpose of statistical analysis.

For the 11 patients whose parents completed the Vineland Adaptive Behavior Scale, total scores were also significantly less than the average range of the normative sample (Vineland Adaptive Behavior Scale Composite: 68.09 ± 21.44 ; $t = -4.94$, $p = .001$) and in a range consistent with their IQ scores. Among these patients, 73% had a score less than 85, and 36% had a score less than 70. Scores were fairly consistent across functional domains (Communication: 72.36 ± 20.54 ; Daily Living Skills: 70.55 ± 28.09 ; and Socialization: 78.91 ± 20.76).

For the 6 patients whose parents completed the Achenbach Child Behavior Checklist, mean scores on the Withdrawn, Anxious/Depressed, Thought Problems, Attention Problems, Delinquent Behavior, and Aggressive Behavior scales were within the average range and not indicative of clinical problems. Scores on the Somatic Complaints (54.83 ± 2.86) and Social Problems (62.20 ± 9.76) scales were higher (i.e., abnormal) than those of the normative sample.

Discussion

Children with neonatal or early infantile brain tumors are a medically challenging group. These infants are a rare subset of patients, and their tumors show variable histologic properties. In addition to the rarity and variability of these tumors, they can also grow quite large (Figure 2). Thus, conducting clinical research that is generalizable to comparable populations is difficult. Also, little is known about this age group because no consensus has been reached on a cutoff age.^{23–28} In prospective studies, patients with neonatal or early infantile brain tumors are typically included in the cohort of patients who are younger than 3 years,^{9–14} making it difficult to draw conclusions about the results of treatment, disease outcome, and morbidity for the subset. Our review of findings published in the Surveillance, Epidemiology, and End Results database⁸ on children younger than 1 year with high-grade glioma or diffuse pontine glioma revealed that these patients may have a better outcome than their older counterparts. Such limited data and incidental case reports of spontaneous regression in a neonatal diffuse pontine glioma²⁹ or cure of neonatal high-grade glioma via surgery only³⁰ provide evidence that, like leukemia^{2,3} and neuroblastoma,⁴ brain tumors that arise during early infancy may have a different biological behavior than in older infants.

More than 50% of our patients were alive at the time of this retrospective review. Survival data from other studies of brain tumors that occur during early infancy have varied from 14% to 58%.^{23–27,31} This difference in survival may be attributed to multiple factors. First, different age groups were included in these studies: at birth,^{23,31} neonatal period,²⁴ up to 2 months of age,^{25,26} and up to 6 months of age.²⁷ Second, surgical mortality was reported in some studies as 35%²⁵ and 43%.²⁶ Third, different therapeutic approaches or the lack of any treatment may have been a factor; many studies deny this age group treatment. For example, Isaacs²³ reported 15% overall survival in a review of 154 cases (54 were stillborn). Of the 100 children born with a brain tumor, 33 received some form of therapy, including surgery only, and out of those 21 patients (63.6%) survived. Another study also reported the tendency to not treat this population.²⁴

Although our cohort is too small to draw any definitive conclusions, this review provides valuable information. First, the survival of infants with cranial neoplasms during early infancy appears to be influenced mostly by the pathology and location of the tumor. This finding supports those from previous studies.^{23, 27, 28, 31} The frequency and degree of late effects on the patients' quality of life was also severe. Most patients suffered some form of neurologic, endocrine, or cognitive late effects.

At a mean of 5 years after diagnosis, most patients had IQ scores indicative of mental retardation. This rate is much higher than that seen in the general population (2%).¹⁸ These findings are particularly concerning, given the known association of cognitive late effects with academic difficulties, unemployment, and diminished quality of life among childhood cancer survivors.^{32,33} In addition to notable deficits in IQ, patients showed substantially impaired adaptive functioning, indicating a decreased ability to independently complete tasks of daily living. Few behavioral problems were noted, with the exception of somatic complaints, which are expected among children with a significant medical history, and social problems, which is consistent with previously published findings.³⁴ Although it appears that the subsample of our patients who participated in neurocognitive assessments was representative of the cohort and other studies have shown similar results, caution should be taken when generalizing these findings to all individuals with a brain tumor in early infancy, given the retrospective nature of this study. Kokunai et al²⁴ reported that 76% of neonates and 73% of children younger than 1 year in their study met the criteria for mental retardation, but no further details were provided. Jooma et al²⁵ reported that all 3 surviving patients from their group of 17 were severely affected, and Lasky et al²⁷ reported 4 of 7 surviving patients had significant neurocognitive and psychomotor complications. Future studies that include prospective, longitudinal cognitive assessments are needed to allow for predictive modeling based on demographic and clinical variables. Identifying the risk factors for cognitive late effects will enable us to modify anticancer treatments, improve monitoring, develop targeted cognitive interventions, and educate parents.

In addition to age at diagnosis, many factors (e.g., late diagnosis, use of aggressive treatment modalities, insertion/revisions of ventriculoperitoneal shunts, and use of cranial radiation therapy) may contribute to the high rate of adverse late effects seen in our survivors. Of the 5 patients in our study who had an IQ $\leq$ 50, only 2 had received radiation therapy. In fact, the patient with the lowest IQ score did not receive radiation therapy.

The rate of ventriculoperitoneal shunt insertion/revision in our study was higher than that previously reported in children with brain tumors. Eighteen of our patients had ventriculoperitoneal shunts, and 11 required at least 1 revision. In 2 previous reports, the rates were 20% for those with posterior fossa tumors³⁵ and 15% for all brain tumors.³⁶ However, previous studies of children younger than 3 years with brain tumors have reported rates of ventriculoperitoneal shunt insertion/revision between 45%¹⁴ and 47%.¹² In a

national study, the rate of ventriculoperitoneal shunt revision for children varied from 20% to 70% among various hospitals.³⁷ Factors associated with increased risk for shunt revision were hospital yearly volume of shunt insertions, shunt type, diagnosis necessitating the shunt, and age of the patient at the time of initial shunt insertion. Revisions were needed for 49% of children who received their first shunt during the neonatal period and for 36% who received a shunt before 1 year of age.

Findings from our data on survival and late effects in this population, in addition to the limited published literature, underscore the need for prospective studies of children with brain tumors in early infancy. Prospective studies will help health care providers and families make informed decisions about whether to pursue aggressive therapy, minimal therapy, or no therapy. These children also need to be treated in specialized centers equipped to deal with the medical and surgical needs of such young patients.

Histologic confirmation is important before any treatment decision is made, due to the pathologic complexity and heterogeneity of brain tumors in early infancy. Increased awareness about neonatal cranial neoplasms will also help healthcare providers improve early diagnosis.^{28,38} Finally, a better biological understanding of these tumors may help identify groups who require observation only or minimal therapy using differentiating agents, as is the case with neuroblastoma¹ and supported by reports of cure with chemotherapy alone in patients with high-grade glioma,¹⁰ the spontaneous regression of tumor in those with diffuse pontine glioma,²⁹ and the differentiation of high-grade glioma into pilocytic astrocytoma in a recently published case.³⁹

Conclusion

Although our study has limitations due to the retrospective collection of data over a long period, possible bias toward referral of high-risk cases to our institution, and the small number of patients included, we believe it underscores the importance of studying children in whom brain tumors arise during early infancy as a unique population in terms of treatment decisions, survival, and late effects.

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Figure 1.

IQ (n=13) and adaptive functioning (i.e., Vineland Adaptive Behavior Scale) (n=11) scores of patients with brain tumors during early infancy. Scores are shown in relation to the criterion for diagnosis of mental retardation. The horizontal line represents the expected 2% rate of IQ scores less than 70 in the general population.

Figure 2.

An axial T1-weighted (A) and coronal T2-weighted (B) images of patient 13 in table 2, at diagnosis. The arrows demonstrate the blood products within the tumor (bright on T1- but dark on T-2 weighted images)

Table 1

Demographic and Clinical Characteristics of the Patient Population

	<i>n</i> (%)
Sex	
Male	12 (44)
Female	15 (56)
Race	
African-American	4 (15)
Caucasian	23 (85)
Age at Diagnosis	
In utero	1 (4)
At birth	2 (7)
Neonatal (< 30 days)	2 (7)
Early infant (30–150 days)	22 (81)
Symptoms at Presentation	
Increased head circumference	14 (52)
Emesis	10 (37)
Seizure activity	8 (30)
Oculovisual abnormalities	7 (26)
Irritability	7 (26)
Decreased appetite	5 (19)
Full fontanelle	5 (19)
Lethargy	3 (11)
Torticollis	3 (11)
Abnormal breathing	3 (11)
Failure to thrive	2 (7)
Insomnia	2 (7)
Motor abnormalities	1 (4)

Table 2

tumor characteristics, treatment modalities and outcome

Pt #	Age at Dx (days)	Tumor Location	Pathology	Surgery at Dx	Adjuvant Therapy	Recurrence extent	Treatment at recurrence	Age (years) at RT/Field	Status/follow-up (years)
1	58	Lt. frontal, parietal, temporal lobes	AA	PR	Chemo, RT	L	Chemo	3.1/parietal-thalamic-hypothalamic	DOD/5.9
2	63	Posterior fossa	FA	GTR	Observe	None	n.a.		NED/21.6
3 ^{a, b}	92	Optic chiasm, hypothalamus, 3 rd ventricle	PA	Bx	Chemo	L+D	Chemo, RT	3.0/CSI	SD/17.2
4 ^a	84	Thalami, midbrain	FA	Bx	Chemo	L	RT	5.4/thalami	SD/11.6
5 ^a	110	Suprasellar, hypothalamus	PA	PR	Observe	L	Chemo		SD/7.0
6	78	Lt. temporal lobe	AA	Bx	Chemo		L+D	GTR, Chemo	DOD/1.6
7	Birth	Posterior fossa	PA	STR	Observe	L+D	GTR, Chemo, RT	1.8/CSI	SD/15.7
8 ^{a, b}	46	Quadrigeminal plate, brainstem, tentorial notch, pineal gland	GBM	GTR	Chemo	L	Chemo, RT	1.1/WB	DOD/1.2
9 ^a	68	Lt. parietal lobe	DIG	STR	Chemo	None	n.a.		NED/0.4
10 ^{a, b}	51	Intraventricular, frontoparietal, 3 rd ventricle	CPC	NTR	Chemo, RT	None	n.a.	2.5/CSI	NED/14.2
11 ^{a, b}	66	Frontal/parietal lobes	CPP	GTR	Observe	L	STR		NED/12.7
12	5	Lateral ventricle	CPC	Bx, NTR ^c	Chemo	None	n.a.		NED/4.0
13 ^a	Birth	Parietal-occipital-temporal	HGG	Bx, GTR	Chemo	None	n.a.		NED/2.1
14	110	Posterior fossa	MB	Bx, STR	Chemo	L+D	Palliation ^d		DOD/0.2
15 ^a	81	Posterior fossa	MB	STR	Chemo	L+D	Chemo		NED/2.1
16 ^{a, b}	In Utero	Pineal gland, 3 rd /4 th ventricles	AE	Bx, GTR	Chemo, RT	None	n.a.	1.1/3 rd ventricle and aqueduct	NED/7.5

Pt #	Age at Dx (days)	Tumor Location	Pathology	Surgery at Dx	Adjuvant Therapy	Recurrence extent	Treatment at recurrence	Age (years) at RT/Field	Status/follow-up (years)
17 ^a	103	Temporal fossa	AE	GTR	Chemo	L	PR, RT	1.2/Temporal fossa	NED/7.5
18 ^a	68	Parietal lobe, supratentorium	AE	STR	Observe	L	NTR, RT	1.0/Temporo-parietal lobe	NED/6.8
19	97	Posterior fossa	AE	STR	Chemo	L	Chemo		DOD/0.4
20	84	Posterior fossa	MB	STR, GTR	Chemo	L+D	Chemo		DOD/1.1
21	57	Intraventricular, posterior atrium	ATRT	Bx, GTR	Chemo	L+D	STR, Chemo		DOD/0.7
22	81	Cerebellar pontine angle, 4 th ventricle, tentorium	ATRT	NTR	Chemo	L	Palliation ^d		DNOD/0.3
23	95	Pineal region, superior vermis, cerebellar cistern	ATRT	Bx	Chemo	L+D	Chemo		DOD/0.8
24	46	Posterior fossa	ATRT	GTR	Chemo	L	Palliation ^d		DOD/0.6
25 ^a	62	Posterior fossa	ATRT	STR	Chemo	L+D	Palliation ^d		DOD/0.6
26	4	Posterior fossa	ATRT	STR, GTR	Chemo	L	Palliation ^d		DNOD/0.3
27	49	Thalamus, temporal parahypothalamus region	MGN	PR, GTR	Observe	None	n.a.		NED/0.5

^aThese patients received neurocognitive assessments.

^bThese patients had an IQ score ≤ 50 ; patient #3 scored 41, and the other 4 were reported as ≤ 50 .

^cThis patient received second-look surgery after 3 cycles of chemotherapy and 8 months after the initial Bx.

^dThese patients received only palliation therapy at recurrence.

Abbreviations: AA, anaplastic astrocytoma; AE, anaplastic ependymoma; ATRT, atypical teratoid rhabdoid tumor; Bx, biopsy; Chemo, chemotherapy; CPC, choroid plexus carcinoma; CPP, choroid plexus papilloma; CSI, craniospinal irradiation; D, distant; DIG, desmoplastic infantile ganglioglioma; DNOD, died but not of disease; DOD, died of disease; Dx, diagnosis; FA, fibrillary astrocytoma; GBM, glioblastoma multiforme; GTR, gross total resection; HGG, high-grade glioma; L, local; Lt., left; MB, medulloblastoma; MGN, mixed glioneuronal; n.a., not applicable; NED: no evidence of disease; NTR, near total resection; PA, pilocytic astrocytoma; PR, partial resection; PT, patient; RT, radiation therapy; SD, stable disease; STR, subtotal resection; WB, whole brain.