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CLINICAL STUDY

Suicide ideation in pediatric and adult survivors of childhood brain tumors

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Abstract Survivors of pediatric brain tumors are at risk for long-term psychological morbidities. The current study investigated the prevalence and predictors of suicide ideation (SI) in a clinical sample of youth and adult survivors. Retrospective chart reviews were completed for 319 survivors of pediatric brain tumors who were assessed via clinical interview during routine neuro-oncology clinic visits between 2003 and 2007. Survivors were, on average, 18.0 years of age (SD = 4.9) and 10 years from diagnosis (SD = 5.0) at their most recent follow-up. The most common diagnosis was low-grade glioma ($n = 162$) followed by embryonal tumors (PNET/medulloblastoma; $n = 64$). Multivariable logistic regression was used to calculate odds ratios (OR) and 95 % confidence intervals (CI) for SI. Nearly 12 % of survivors (11.7 %, $n = 37$) reported SI. Five survivors (1.5 %) had documented suicide attempts, though none were fatal. In a multivariable model, adjusting for sex and age, history of depression (OR = 20.6, 95 % CI = 4.2–101.1), psychoactive medication treatment (OR = 4.5, 95 % CI = 1.8–11.2), observation or surgery only treatment (OR = 3.7, 95 % CI = 1.5–9.1), and seizures (OR = 3.6, 95 % CI = 1.1–11.1) were significantly associated with SI in survivors. Survivors of pediatric brain tumors appear to be at risk for experiencing SI. Our results underscore the importance of a multidisciplinary approach to providing follow-up care for childhood brain tumor survivors, including routine psychological screenings.

Keywords CNS tumors · Suicide · Survivorship

Introduction

Malignancies of the central nervous system (CNS) account for nearly 20 % of pediatric cancers with an incidence of approximately 3.0 per 100,000 persons in the United States [1]. While over 70 % of children diagnosed with brain tumors achieve long-term survival, the consequences of tumor location within the CNS are considerable. Musculoskeletal, endocrine, and neurologic complications are frequently reported [2]. In addition, evidence suggests that brain tumor survivors are at heightened risk for psychological morbidities, including depression, anxiety, and social dysfunction [3–5].

Suicidal behavior is a potential manifestation of psychological distress. Suicide is a major public health concern and the significance of this problem is underscored by national mortality statistics indicating that it is a leading cause of death among individuals 10–34 years of age [6]. The lifetime prevalence of suicide ideation (SI) in US adolescents (13–18 years of age) has been estimated at 12.1 %, with approximately 4 % reporting plans and

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attempts [7]. Among US adults (≥18 years of age), 3.7 % reported suicidal thoughts between 2008 and 2009 while 1 % reported making a plan and 0.5 % reported an attempt [8]. Population-based studies of patients diagnosed with cancer have reported standardized mortality ratios (SMR) for suicide deaths ranging from 1.3 to 2.9, yet these studies have not differentiated between pediatric and adult cancer patients [9–11]. Studies of mortality in survivors of childhood cancer have not reported increased risk of suicide relative to the risk observed in matched-populations [12–15].

Suicide ideation (SI) and previous attempts have been identified as salient risk factors of completed suicide. Elevated rates of SI within cohorts of adult survivors of childhood cancer have been reported [16, 17]. Recklitis et al. [16] reported that 12.8 % of 226 adult survivors of childhood malignancies reported current SI or past attempts. Younger age at diagnosis and cranial radiation treatment were associated with greater likelihood of suicidality, though this sample did not include brain tumor survivors. More recently, data from the Childhood Cancer Survivor Study (CCSS), indicated that 7.8 % of adult survivors reported SI compared with 4.6 % of sibling controls [17]. SI was significantly associated with CNS malignancy, with nearly 11 % of CNS tumor survivors reporting SI. Depression, pain and poor physical health were associated with increased likelihood of SI.

Taken together, these data and the well-documented physical, neurologic, and psychological late effects observed in survivors of childhood brain tumors suggest that this subgroup of survivors may be especially vulnerable to suicidality. To our knowledge, this is the first study to report on SI in a sample of youth and adult survivors of pediatric brain tumors.

Methods

Retrospective chart review

A medical record review of survivors of pediatric brain tumors followed by the Pediatric Neuro-Oncology Outcomes Program at Dana-Farber Cancer Institute (DFCI) and Children's Hospital Boston (CHB) was completed with approval from the Institutional Review Board. All brain tumor patients treated at DFCI/CHB are referred to the Outcomes Program 2 years post-treatment completion. Clinical care involves a multidisciplinary approach including routine physical, neurological, and psychological assessments. Demographic, disease, and treatment-related data were abstracted from medical records. Pre-morbid medical conditions, pre-operative hydrocephalus, and peri-operative complications were abstracted when documented in the medical record. Information regarding psychological status, including SI was obtained from structured psychological screenings completed by licensed clinical psychologists.

Assessment of suicide ideation

As a part of the routine follow-up care provided in the neuro-oncology clinic, all patients were assessed via a semi-structured clinical interview, developed by our group, based on the criteria set forth by the DSM IV-TR [18]. This interview included assessment of depression, anxiety, behavior, and social functioning. Patients reported as depressed met criteria based on symptoms including low mood/irritability, appetite disturbance, anhedonia, sleep disturbance, and helplessness/hopelessness. Anxiety included symptoms of intrusive thoughts, nervousness, obsessive thinking, and panic attacks. Behavior difficulties included symptoms of pervasive developmental disorders, attention-deficit/hyperactivity disorder, oppositional defiant disorder, and conduct disorder. Social difficulties included behaviors such as difficulty establishing or maintaining friendships, social isolation or exclusion from peer groups, and teasing or bullying. In a standard clinical interview, intensity, duration and frequency of psychological symptoms were assessed. SI was only assessed when clinically indicated (e.g. presence of hopelessness) and was defined as any endorsement of thoughts of ending one's life, including both passive and active ideation. Thus, not all patients underwent assessment of SI. SI was coded as present or absent based on patient report of SI at time of their clinic visit, though recall was not limited to a specific time interval (e.g. past 7 days). Suicide attempt was defined as any physical act aimed toward inflicting self-harm with the reported intent to end one's life.

Patient population

Four hundred ten unique patients were seen in the Neuro-Oncology Outcomes Program between January 2003 and September 2007, of whom 391 (95.4 %) were evaluated by a licensed clinical psychologist. Patients were eligible for inclusion in the current study if they were diagnosed with a primary brain tumor before 20 years of age and were older than 10 years of age at the time of their most recent clinic visit. This resulted in 319 patients (77.8 %) with medical record data available for review.

Statistical analyses

Descriptive statistics for demographic, disease and treatment variables are reported. For SI, cases and non-cases were compared on potential risk factors using independent

sample t tests for continuous variables. Chi square and Fisher's exact tests were used to compare discrete variables. Logistic regression models were used to adjust for age and sex with odds ratios (OR) and 95 % confidence intervals (CI) reported for SI. Only variables with significant contributions ($p < 0.10$) in univariate analyses were considered for inclusion in the final multivariable model. Multicollinearity was examined among all predictors and covariates. Given the potential confound between diagnosis and treatment variables, these variables were not simultaneously included in the multivariable logistic regression model and the final logistic regression model includes only treatment information. Similarly, due to the small number of patients with the observed outcome of SI only a select number of variables were included as predictors in the final regression model. Specifically, the presence of depressive symptoms was selected for inclusion in the final model as this is a salient risk factor of suicidality in the general population.

Results

Survivors ranged in age from 10 to 35 years (M = 18.0, SD = 5.0) at the time of their most recent follow-up visit. Fifty-one percent of survivors were ≥18 years of age at follow-up. Approximately 40 % of survivors were ≥10 years from diagnosis. The most common diagnosis was low-grade glioma followed by embryonal tumors (PNET/Medulloblastoma). Thirty-one percent of survivors were treated with surgical resection alone (i.e. complete or subtotal resection with no further treatment) or followed by observation, 61 % received cranial radiation therapy, and 36 % received chemotherapy. Additional characteristics of the survivors are provided in Table 1.

Nine hundred twenty five psychological screenings were completed over the study inclusion period with an average of three assessments completed per survivor. History of SI was unrelated to number of psychological screenings completed. Thirty-seven patients (11.7 %) reported SI during at least one clinic visit and 3 reported SI at more than one screening. Five patients (1.6 %) had documented suicide attempts, two of whom reported ideation at multiple screenings. None of these attempts were lethal, though four patients were hospitalized for inpatient psychiatric care and one patient was evaluated in a local emergency department without inpatient admission. All five patients had a history of depression, though data to establish a temporal relationship between the onset of depression and suicidality were unavailable.

Age at the time of SI was available for 35 of 37 patients. Mean age at time of SI was 16.9 years (range 7–26 years). We analyzed the associations between demographic, disease and treatment variables and SI for the entire sample. Independent sample t tests comparing cases and non-cases yielded significant associations between SI and older age at diagnosis ($p = 0.017$) and older age at follow-up ($p = 0.007$) (Table 2). SI was unrelated to sex, tumor location, time since diagnosis, disease recurrence/progression, post-operative posterior fossa syndrome, or other medical complications in unadjusted analyses (Table 3). Psychological morbidities were significantly associated

Table 1 Demographic and clinical characteristics of survivors ($n = 319$)

	Mean	SD
Age at most recent follow-up	18.0	4.9
Age at diagnosis	8.0	4.9
Years since diagnosis	10.0	5.0
	N	%
Sex		
Male	143	44.8
Female	176	55.2
Tumor location		
Posterior fossa/cerebellum	110	34.5
Diencephalon/brain stem	99	31.0
Cerebral cortex	110	34.5
Diagnosis		
Low grade glioma	162	50.8
Embryonal tumor	64	20.1
Craniopharyngioma	23	7.2
Germ cell tumor	28	8.8
Ependymoma	14	4.4
Other	28	8.8
Treatment		
Surgery only (observation)	99	31.0
Surgery + radiation	95	29.8
Surgery, radiation + chemotherapy	84	26.3
Other	41	12.9
Medical complications		
Hydrocephalus[a]	114	51.4
Seizures	53	16.6
Neurofibromatosis	21	6.6
Posterior fossa syndrome	14	4.4
Disease recurrence/progression	75	23.6
Psychosocial complications		
Depression	130	40.8
Anxiety	88	27.6
Social problems	147	46.1
Behavior problems	70	21.9
Psychoactive medications[b]	72	23.7

[a] Data available for $n = 222$

[b] Data available for $n = 303$

Table 2 Comparison of suicidal and nonsuicidal survivors

	Suicidal ($n = 37$)		Nonsuicidal ($n = 279$)		Suicidal vs. Nonsuicidal	
	M	SD	M	SD	T-statistic	p value
Age at follow-up	20.0	5.0	17.1	4.8	2.72	0.007
Age at diagnosis	9.8	4.7	7.7	4.8	2.41	0.017
Years since diagnosis	9.8	6.6	9.5	4.8	0.31	0.76

Table 3 Suicide ideation in survivors of pediatric brain tumors

	Total N ($N = 316$)	SI in survivors		Chi square p value
		N	%	
Sex				0.57
Male	142	15	10.6	
Female	174	22	12.6	
Tumor location				0.30
Cerebral cortex	108	9	8.3	
Posterior fossa	110	13	11.8	
Diencephalon	98	15	15.3	
Surgery only treatment[a]				0.004
Yes	97	19	19.6	
No	219	18	8.2	
Cranial radiation				0.04
Yes	195	17	8.7	
No	121	20	16.5	
Seizures				0.07
Yes	53	10	18.9	
No	263	27	10.3	
Disease recurrence				0.56
Yes	73	10	13.7	
No	242	27	11.2	
Depression[b]				<0.001
Yes	127	35	27.6	
No	189	2	1.1	
Anxiety				<0.001
Yes	86	23	26.7	
No	230	14	6.1	
Psychoactive medication				<0.001
Yes	70	26	37.1	
No	230	11	4.8	
Social problems				0.07
Yes	144	22	15.3	
No	172	15	8.7	
Behavior problems				0.003
Yes	68	15	22.1	
No	248	22	8.9	

[a] Includes patients treated with surgical resection or followed by observation alone

[b] Fisher's exact test

with a history of SI. Specifically, in analyses adjusting for age and sex, history of depression (OR = 35.9, 95 % CI 8.4–153.8, $p < 0.001$), anxiety (OR = 8.6, 95 % CI 3.8–19.5, $p < 0.001$), behavior problems (OR = 3.5, 95 % CI 1.6–7.4, $p = 0.001$), and social problems (OR = 2.1, 95 % CI 1.03–4.4, $p = 0.04$) were significantly associated

Table 4 Logistic regression analysis for suicide ideation

	χ^2 step	Model R^2	Final OR	95 % CI
Step 1	6.99	0.044		
Female sex			1.6	0.7–3.8
Current age			1.1	0.99–1.2
Step 2	66.46	0.41		
Depression history			20.5	4.2–101.1
Psychoactive medication			4.5	1.8–11.2
Step 3	12.93	0.48		
Age at diagnosis			1.1	0.97–1.2
Surgery only treatment[a]			3.7	1.5–9.1
Seizures			3.6	1.1–11.1

[a] Includes patients treated with surgical resection or followed by observation alone

with SI. Patients with a history of psychotropic medication treatment were 12 times more likely to have a history of SI than those who did not have documented treatment with psychoactive medications (OR = 12.6, 95 % CI 5.7–28.0, $p < 0.001$). After adjusting for sex and age, survivors followed by observation or treated with surgical resection alone were 3.5 times more likely to have a history of SI compared with survivors treated with other modalities, including cranial radiation therapy (OR = 3.5, 95 % CI 1.7–7.4, $p = 0.001$). We further divided surgery into the following categories: none/biopsy ($n = 15$), subtotal or near total resection ($n = 31$), and gross total resection ($n = 50$). SI did not differ significantly by surgery group.

Hierarchical multivariable logistic regression analysis was performed to examine if SI in survivors was independently associated with medical variables after accounting for demographic (step 1) and mental health factors (step 2) (Table 4). Entry of medical variables in the last step of the model significantly improved model fit ($p = 0.005$). In the final model, SI was significantly associated with history of depression (OR = 20.5, 95 % CI 4.2–101.1, $p < 0.001$), psychoactive medication use (OR = 4.5, 95 % CI 1.8–11.2, $p = 0.001$), observation or surgery only treatment (OR = 3.7, 95 % CI 1.5–9.1, $p = 0.004$), and history of seizures (OR = 3.6, 95 % CI 1.1–11.1, $p = 0.029$). The final model accounted for 47.5 % of the variability in SI and the Hosmer–Lemeshow test was nonsignificant ($\chi^2 = 6.82$, $p = 0.56$), indicating good model fit.

Conclusions

A significant proportion of pediatric brain tumor survivors reported SI (11.7 %) during a routine follow-up visit to a late effects clinic. This is appreciably higher than the 12 month SI prevalence of 3.7 % in the general US adult population [8]. However, our finding is consistent with a recent CCSS report which indicated that 10.6 % of adult survivors of childhood CNS tumors reported SI using a 7 day recall period. While methodological differences, including sampling intervals and approach toward assessment of SI, preclude direct comparison across studies, the number of survivors endorsing SI is concerning and highlights a potentially serious consequence of psychological distress following treatment for childhood brain tumors.

We found SI to be significantly associated with mental health variables, treatment modality, and history of seizures. History of depression was the strongest predictor of SI in our sample. This finding is not unexpected as mood disorders are one of the strongest predictors of suicidal behavior in the general population [19, 20], as over 90 % of persons who complete suicide may have a psychiatric illness at the time of death [21, 22]. Recent data from the National Comorbidity Survey Replication revealed that 66 % of US adults with suicidal thoughts, 77.5 % with a plan, and 79.6 % who make attempts have a prior mental health disorder [20]. Importantly, we must note potential bias influencing the results of our study, as patients endorsing depressive symptomatology were more likely to be screened for SI.

Survivors with a history of treatment with psychoactive medication were 4.5 times more likely to report SI after adjusting for history of depressive symptoms. We do not attribute SI to specific psychoactive medication use; rather, we speculate that survivors treated pharmacologically had more complex mental health issues which were associated with SI. However, the relationship between psychoactive medications and suicidality in cancer survivors may warrant further investigation as the FDA has issued warnings regarding increased risk for SI and behavior following treatment with select antidepressant and antiepileptic medications [23, 24]. Ideally, the pharmacologic management of psychiatric symptoms in cancer survivors would involve a trained mental health professional (i.e. psychiatrists).

We also found that recurrent/refractory seizures were associated with SI in this sample of survivors. After adjusting for mental health variables, survivors with a history of seizures were 3.5 times more likely to report a history of SI. Nineteen percent of survivors with seizures reported SI compared to 10 % of survivors without seizures. While not anticipated, this finding is consistent with past studies reporting increased risk of suicide in patients with epilepsy [25, 26]. However, given the small number of patients with seizures, and even smaller number reporting SI, our finding must be interpreted with caution and likely cannot be generalized beyond the current sample. Moreover, we did not have information related to treatment for seizure disorders at the time of SI.

Survivors followed by observation or treated with surgery alone were more likely to report SI than those treated

with other modalities. Surgery only treatment has been associated with high rates of psychosocial morbidities in low-grade glioma survivors [27, 28], suggesting that the late effects for these patients may be greater than previously appreciated. This is consistent with reports that survivors of low-grade glioma experience long-term morbidity related to their disease and treatment and that such tumors are not benign with respect to neurologic sequelae [29, 30]. Our group also recently reported that survivors of low-grade gliomas report more pain compared to survivors of other childhood brain tumors [31]. Importantly, Recklitis et al. [17] identified pain as a significant predictor of SI in adult survivors of childhood cancer. The contribution of pain to suicidality in low-grade glioma survivors appears to warrant further investigation. That SI was unrelated to cranial radiation therapy is consistent with a report from CCCS which revealed that radiation to the head/brain was not significantly associated with SI in adult survivors [17]. Alternatively, at our institution, patients treated with surgery only receive less routine psychological follow-up compared to patients treated with radiation therapy, and thus psychological morbidities may go undetected for untreated for longer periods of time. Though speculative, it may be that survivors treated with cranial radiation, who presumably experience greater neurocognitive impairment, do not recognize the extent of the morbidities associated with their disease/treatment and experience lower levels of associated distress. Future studies should explore severity of cognitive impairment and psychological distress in this patient population.

Fewer than 2 % of survivors in our study reported previous suicide attempts. This is slightly lower than the 4 % of adult participants who reported attempts in a previous study of adult survivors of childhood cancer [16]. Epidemiologic data on lifetime prevalence of attempts indicate that 4.1 % of adolescents and 0.6 % of adults report suicide attempts [7]. Notably, each patient in our study with documented suicide attempts had a previous history of SI. This highlights the need for close monitoring of patients who endorse ideation. In the general population, one-third of individuals with SI make a plan, 72 % of those with a plan make an attempt, and 26 % move directly from ideation to an unplanned attempt [32]. Importantly, SI is often transient and may recur at varying time intervals [33, 34]. Such variability, which may reflect mood lability, has been identified as a predictor of attempt status in young adults [35].

Our results must be interpreted in the context of several limitations. First, this study is retrospective in nature and data abstracted from medical charts may not represent the true prevalence of psychological or medical late-effects. Second, the psychological assessment involved a semi-structured clinical interview developed by our institution, which is not validated for the assessment of psychological/psychiatric symptoms, and we did not employ standardized measures of psychological functioning. Recklitis et al. [36] have demonstrated the utility of using psychological screening instruments to assess suicidality in the pediatric cancer survivor population. Ideally, a multi-method assessment approach involving a clinical interview and standardized measure would be employed when assessing psychological late effects. Third, simply documenting the presence or absence of suicidal ideation does not provide information regarding the severity or intensity of such thoughts. Our methodological approach limits our ability to assess temporal relationships between psychological symptoms, medical variables and SI. We must acknowledge the selection bias in our sample. Our multidisciplinary clinic often follows patients who have complex medical, learning and psychosocial issues and it is possible that these data overestimate the prevalence of SI or mental health conditions experienced by survivors of pediatric brain tumors. However, because SI was only assessed as clinically indicated and that the time frame that participants experienced SI was not systematically reported, we speculate that our methodological approach may have resulted in an underestimate of the prevalence of SI. Moreover, SI is often transient in nature and may be absent during a clinical interview yet resurface at a later time. Finally, we do not have data on a control population which limits our ability to discuss the prevalence of SI in relation to the general population or survivors of other childhood malignancies.

Despite these limitations, our results make an important contribution to the growing literature on psychosocial late effects experienced by survivors of pediatric brain tumors. Our findings support recent reports that suicidality is a serious and unfortunately prevalent issue among these survivors. Such results underscore the importance of a multidisciplinary approach to providing follow-up care for childhood cancer survivors, including routine psychological screenings. Future studies should consider the impact of long-term chronic health conditions in relation to psychological distress and SI in this patient population.

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Conflict of interest The authors have no conflicts of interest to disclose.

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