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Original Article

Hemorrhagic and Ischemic Stroke in Children With Cancer

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ABSTRACT

BACKGROUND: Adult survivors of childhood cancer have an increased risk of cerebrovascular disease; little is known about early stroke risk in childhood cancer. Our objectives were to assess stroke prevalence in children with cancer, to establish cancer and stroke type, and to determine if modifiable risk factors for stroke were present. **METHODS:** Children with stroke and cancer were compared with all children seen for cancer at a single institution between 2000 and 2009. An International Classification of Disease, 9th version, code search and search of existing pediatric oncology and stroke databases identified children <18 years with ischemic stroke, intracerebral hemorrhage, and cerebral sinovenous thrombosis. **RESULTS:** Of 1411 children with cancer, 15 had a stroke (1.1%, 95% CI: 0.6-1.7%). Stroke classifications were seven intracerebral hemorrhages, five ischemic strokes (one of which was followed by intracerebral hemorrhage), and three sinovenous thromboses. Stroke occurred at a median of 5 months after cancer diagnosis. Ten children with strokes had hematologic malignancies and five had brain tumors. Thirteen patients died poststroke, eight because of withdrawal of care. White blood cell count $\geq$48,000/mm^3 was found in four children, all with intracerebral hemorrhage. Five of seven children with intracerebral hemorrhage had platelets <50,000/mm^3. **CONCLUSIONS:** Stroke has a prevalence of approximately 1% in children with cancer. Hemorrhagic stroke and ischemic stroke occur with approximately equal frequency; children with leukemia and brain tumors are at greatest risk.

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Introduction

Strokes result in increased morbidity and a high need for critical care services and are a known complication in patients with cancer.[1] Recent literature has demonstrated that adult survivors of childhood cancer have an increased risk of cerebrovascular disease.[2-7]

The Children's Oncology Group report on cerebrovascular disease in childhood cancer survivors showed that stroke risk is increased in survivors of pediatric central nervous system (CNS) tumors, Hodgkin lymphoma, and acute lymphoblastic leukemia (ALL) who received radiation to the brain and/or neck.[7] Specifically, the relative risk of stroke for leukemia survivors compared with sibling controls was 6.4 at a median of 9.8 years from cancer diagnosis; the relative risk of stroke for brain tumor survivors compared with siblings was 29 at a median of 13.9 years from cancer diagnosis.[3] Similarly, Campen et al. found that the incidence of neurovascular events in pediatric brain tumor survivors is 100-fold higher than in the general pediatric population and that cranial irradiation is an important risk factor.[8] Haddy et al. found that among 5-year survivors of childhood cancer, the radiation dose to the brain during radiotherapy was significantly associated with long-term cerebrovascular mortality, namely children who received >50 Gy had a 17.8-fold higher hazard ratio of death from cerebrovascular disease at a median follow-up of 29 years.[5]

However, little is known about stroke risk within the first 5 years after diagnosis of childhood cancer. Packer et al.

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retrospectively analyzed 700 children newly diagnosed with systemic malignancy between 1979 and 1983 and found that 26 children had suffered cerebrovascular accidents (4%), but children with primary intracranial neoplasms were excluded.[9] Bowers et al. performed a 15-year retrospective review of 807 children with CNS tumors and found that 13 children (1.6%) suffered a non-perioperative stroke, defined as a new ischemic brain lesion.[10] In a 7-year retrospective analysis of 85 children with nontraumatic intracranial hemorrhage, Lo et al. found a higher than previously reported frequency of complex chronic illnesses, including 13 brain tumors (15%), as risk factors for pediatric intracranial hemorrhages.[11] Kyrnetskiy et al. identified 51 children with cancer and intracranial hemorrhages, which included subdural, epidural, subarachnoid, and intracerebral (parenchymal or intraventricular) hemorrhages, in an 18-year retrospective review and found 30 children with brain tumors, 19 with leukemia and two with lymphoma.[12] There is literature focusing on stroke in children with selected neoplasms (either leukemia, specifically ALL, or brain tumors),[13-15] or characterizing single stroke type (intracerebral hemorrhage [ICH], ischemic stroke, or cerebral sinovenous thrombosis [CSVT]) in children with cancer.[12,16,17]

Our primary goals were (1) to assess the prevalence of stroke in children with all types of cancer, (2) to determine which children with cancer were most likely to have early stroke and assess stroke type, and (3) to determine whether stroke was simply a complication of aggressive cancer or if modifiable risk factors were present.

Study Design and Methods

We performed a retrospective review of children with ICH, ischemic stroke, and CSVT who were also diagnosed with cancer and followed at a large pediatric tertiary care center. An arterial distribution of ischemic stroke was not required. Watershed and venous infarctions were included, as was ischemic injury resulting from leukemia of the CNS. ICH was defined as parenchymal and/or intraventricular hemorrhage.

To identify children with stroke, an International Classification of Disease, 9th version (ICD-9), code search of medical records was performed using codes for ICH, ischemic stroke, and CSVT. Upon reviewing the existing literature on accuracy and yield of ICD-9 codes for identifying children with stroke[18,19] as well as our institution's billing practices, we selected 14 ICD-9 codes: 325, 342, 430, 431, 432.9, 433, 434, 435, 436, 437, 438, 671.5, 747.81, and 767. For codes in which no decimal places were included, our ICD-9 search included all variations (e.g., 437 includes 437.XX). We also searched existing pediatric oncology and pediatric stroke databases at our center for children diagnosed with both stroke and cancer.

Children younger than 18 years of age seen between January 1, 2000, and December 31, 2009, were included. We excluded children with intratumoral hemorrhage, traumatic hemorrhage, subdural and epidural hemorrhage (typically classified as intracranial hemorrhage, not ICH), and bleeding related to surgical interventions. We abstracted information from the chart on patient demographics (age, sex, race/ethnicity), stroke type and potential etiologies, clinical features at presentation, time from cancer diagnosis to presentation, radiology reports, risk factors for stroke, such as abnormal platelet count and leukocyte count, and coagulation studies at the time of stroke, including disseminated intravascular coagulation (DIC), treatment (for cancer and stroke) including surgical treatment, length of follow-up, and outcome.

Coagulopathy was defined as abnormal coagulation studies: prothrombin time (PT), international normalized ratio (INR) and activated partial thromboplastin time. We defined coagulopathy using an INR >1.5, a PT >18 seconds, or an activated partial thromboplastin time >60 seconds, which is consistent with definitions used in previously published studies on acute traumatic coagulopathy, because there are no standard definitions in children with cancer.[20,21] Because there is no gold standard for the diagnosis of DIC, we adapted the International Society of Thrombosis and Hemostasis DIC scoring system using a combination of prolonged PT or INR, hypofibrinogenemia (when an abnormal fibrinogen level was documented), and thrombocytopenia in the appropriate clinical setting.[22-24] Stroke was defined as documented clinical presentation consistent with stroke such as a focal neurological deficit of sudden onset and radiographic image(s), magnetic resonance imaging, or computed tomography showing cerebral parenchymal infarct(s) or ICH corresponding to the clinical manifestations.[25,26] A pediatric neurologist with expertise in stroke reviewed the abstracted clinical information and neuroimaging to confirm strokes. A pediatric oncologist reviewed all abstracted clinical information to confirm cancer diagnoses. Children with more than one cancer type were classified according to the type of malignancy present at the time of stroke diagnosis. To define a denominator for period prevalence (how many children with cancer had stroke during the study period),[27] oncology billing records were searched for new pediatric patients <18 years of age seen in our center for cancer care with at least two visits between January 1, 2000, and December 31, 2009. The time between first and last visit was calculated to define the duration of follow-up for each child.

All comparisons of proportions were analyzed using chi-square tests or Fisher exact tests when any value was lower than 5. Confidence intervals were calculated by exact methods. We conducted analyses using STATA 11.0 (College Station, TX) and considered a two-sided P value of <0.05 to be significant for all analyses. This study was approved by the Institutional Review Board.

Results

Our initial ICD-9 code search produced 298 records. Upon chart review, 254 children had either a documented ischemic stroke or some type of intracranial hemorrhage (including subdural and epidural hemorrhages), whereas 44 children were incorrectly coded and had a different diagnosis. Among the 254 children, 189 had ICH (parenchymal or intraventricular hemorrhage), 38 had an ischemic stroke, and 27 had CSVT. Thirty-one of these 254 children also had cancer. The institutional pediatric stroke database and pediatric cancer database were also searched and three additional children with cancer and stroke who met the study inclusion criteria were identified. We then